EVALUATION OF REPRODUCTIVE FUNCTION FOR PATIENTS WITH CHRONIC RADIATION SICKNESS

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Introduction: Substantiation of the Study (Radiation Effects on Reproductive Function in the Human: the State of Art)

The reproductive function or the function of population reproduction on which the birth of viable offspring depends implies normally functioning parental endocrine system, primarily gonadal glands, marriage, conception, gestation and delivery of normal children.

Reproductive system is believed to be one of the body systems which show the highest sensitivity to ionizing radiation. It is stated in the ICRP recommendations addressing deterministic radiation effects that exposure doses of 0.15 Gy to male gonads and of 0.65 Gy to female gonads may result in a transient sterility, while in acute exposure at doses of 2-3 Gy persistent sterility is observed [1].

Atrophy of ovaries associated with X-ray irradiation at significant doses was registered in experimental studies as early as the beginning of the XX century [2]. More recent elaborate experiments in animals and clinical observations have clearly demonstrated that ionizing radiation causes degenerative and atrophic changes in the genital glands. Similar to primary ovarian follicles, the spermatogenic epithelium consists of actively dividing cells, and this feature of the tissues pre-determines the prevalence of direct effects of radiation injury, proportional to exposure rates.

Genetic radiation effects associated with germentative cells lead to an increase in the number of individuals with chromosome and gene pathology among the offspring of exposed parents. Registration of genotypical manifestations of this pathology presents considerable difficulties both because of complexity of methods, and the need to "catch a rare phenomenon" in a numerically limited population composing the offspring of exposed residents. That is why, in order to be able to form an idea about the injury to the reproductive function inflicted by radiation exposure, the "phylogenetic approach" is most commonly taken, i.e., recourse is made to the analysis of the phenotypical manifestations of the pathologic condition.

Data on natural incidence of such pathologic conditions as well as risk associated with radiation exposure are cited in the reviews of UNSCEAR [3, 4]. The natural incidence of autosome-dominant and X-linked diseases has been estimated as 1 case per 100 neonates, i.e., 1%. In radiation exposure the incidence increases proportional to exposure dose. The exposure effect of 1remwas found to account for 15-20 excess cases per 1 million neonates in the first generation. It means that 6 excess cases of diseases associated with autosome-dominant and X-linked diseases can be expected to occur in the offspring cohort numbering 10,000, at parental gonadal doses approaching 0.3 Gy.

The spontaneous incidence of recessive diseases was estimated as 11 cases per 10,000 neonates. However, recurring recessive mutations do not become manifested in case of heterozygosis due to which the risk of recessive disease occurrence is small in radiation exposure.

The frequency of chromosome abnormalities among liveborns accounts for 0.4-0.6%. Sufficiently clear-cut diagnostic criteria have now been established for most common chromosome diseases: Down's syndrome, Kleinfelter's syndrome, Shereshevsky-Turner syndrome, X trisomy. The process of chromosome disjunction is rather sensitive to ionizing radiation. If we assume that exposure at the dose of 1remcan lead to the occurrence of 20 additional cases of chromosome diseases per one million newborns, we should expect 6 additional disease cases in the offspring of parents with gonadal dose of 30 rem.

A low incidence of genetic effects in a numerically limited cohort comprising offspring of exposed parents, and the unlikelihood of their being detected on the basis of natural prevalence of these diseases makes us resort to the study of conditions characterized by a higher prevalence and a lesser mutational component, e.g., such pathological conditions as spontaneous abortions, stillbirths, early antenatal death, birth of children with developmental defects. These diseases can be defined as multifactor pathology, often of an unidentified etiology. It is exceedingly difficult to class their causes among genetic and environmental factors.

Nevertheless, a number of authors assume that about 50% of spontaneous abortions are due to genetic causes [5]. In the structure of causes responsible for stillbirth congenital developmental defects may account for 7.5%. Congenital developmental defects may account for 14% in the structure of causative factors of early neonatal death [6]. According to the opinion expressed by some researchers, the incidence of birth of children with developmental defects provides basis for assessment of intensity of the mutational processes [5, 7]. Diseases assigned to the category of developmental defects or congenital abnormalities represent a group of multifactor diseases. The incidence of these diseases is 9% based on the British Columbia Registry, and 6% according to the data on North Ireland. Currently, it is assumed that the mutational component of these diseases makes up 5% [3], however, some authors assume it to be much higher up to 60% [8, 9].

The researchers of the Institute for General Genetics [10, 11], Russia, have substantiated the possibility for genetic monitoring based on morphogenetic signs and analysis of anthropomorphic signs in newborns, in particular. In cases of prevailing influence of mutation it is likely that the balanced process will be transformed into a vectorized genetic one, which should be accompanied by deviations of commonly observed normal distributions.

In addition to the methods listed above some researchers [12] consider that one of the informative methods for radiation-related genetic effects is the estimation of sex ratio for the offspring of exposed persons.

A considerable contribution to the understanding of radiation-induced injury sustained by the reproductive system resulted from the follow-up of a cohort comprising women-survivors of atomic bombardment in Hiroshima and Nagasaki [13, 14]. It was established that the incidence of transient amenorrhea following radiation exposure was proportional to the distance from the hypocenter of the explosion. The higher the exposure dose to ovaries the younger was the age at menopause. However, no difference was noted between the exposed and control populations with regard to fertility, spontaneous abortions and stillbirth rates.

A number of Russian authors described the status of genital organs among women-roentgenologists and radiochemical plant employees exposed to external gamma-radiation resulting in ^{239}Pu body intakes [15-17]. A chronic irradiation at aggregate doses of less than 400 rads led to an increased incidence of unstable hypo- and oligomenorrhea, but it did not affect the course of pregnancy and labor. Women who developed chronic radiation sickness were noted to have spontaneous abortions with higher frequency.

The studies on the incidence of intrauterine fetal loss and analysis of sex ratio were performed for children born to A-bomb survivors in Hiroshima and Nagasaki [18]. These studies did not disclose any differences between the exposed and control populations in the rates of stillbirth, neonatal death, congenital abnormalities in neonates. At the same time, an increased rate of birth of children with small head size and delayed mental development was noted in cases when acute exposure occurred at the 10-18 gestation weeks [19, 20]. An absolute increase in numerical sex ratio of over 4% was noted in case father was exposed, and an absolute increase in numerical sex ratio of over 1.6% [21] was noted in case mothers were exposed, for offspring of A-bomb survivors. On the basis of studies on death rates for children of A-bomb survivors a calculation of the minimum gamet doubling-dose was made for mutations causing death during the first 17 years of life. It was estimated as 46 rem for exposed fathers, and 125 rem for exposed mothers [22].

In our earlier studies addressing the status of reproductive function for the population of the South Urals we analyzed the outcomes of 2,460 pregnancies for exposed and unexposed persons [23] on the basis of retrospective data from obstetric histories. However, these studies did not involve analysis of the group encompassing patients with chronic radiation sickness (CRS).

Thus, an overview of literature data shows that clinical and epidemiological followup studies focusing on the post-exposure status of reproductive function are few, and their results are rather contradicting. All the foregoing stresses the expediency of studies aiming at assessment of chronic radiation effects on reproductive function in patients with CRS, and the Techa riverside residents exposed at a wide range of doses.

Chapter I. Follow-up Cohort and Methods of Study

1.1. A brief characterization of radiation conditions in villages on the Techa and estimates of gonadal doses for residents

Radiation conditions in the Techa riverside villages were described in detail in publication [24-26]. In the present report it was deemed necessary to dwell on certain aspects of gonadal dose estimation for exposed residents in the present report.

Radiation exposure of the Techa riverside residents occurred as a result of the operation since 1948 of a military plutonium processing plant located within 100 km of Chelyabinsk city in the Urals. In the early period (1949-1956) of the facility's operation the problem of radioactive waste disposal was not solved, thus, high- and medium-level wastes from the radiochemical plant were dumped into the Techa-Iset-Tobol river system. In this period $7.6x10^{7}$ m^{3} liquid wastes with total activity of 10^{17} Bq ($2.75x10^{6}$ Ci) were discharged into the river. In the overall isotope composition of the released wastes the combined contents of ^{89}Sr and ^{90}Sr accounted for 20.4%, and that of ^{137}Cs for 12.2%. About 95% of the total activity were released into the river in the period from March 1950 to November 1951. The average daily discharge rate was estimated to be $1.6x10^{14}$ Bq (4,300 Ci) during that period.

At the time of radioactive waste discharges 39 villages with a total population of 26.5 thousand were located on the banks of the Techa all the way to its falling into the Iset. The population had not been warned about the radioactive waste discharges into the river, and a large proportion of residents were using river water for drinking, cooking and other domestic needs.

It is due to these circumstances, that the residents of the Techa riverside were exposed to both external and internal radiation. External radiation is attributed to a high gamma-background on the river banks, in the villages and inside houses. Internal radiation resulted from consumption of river water and foodstuffs produced in the area. Internal exposure doses accumulated due to body intakes of osteotropic radionuclides of strontium, and uniformly distributed ^{137}Cs .

1.1.1 Gonadal doses

The focus of the present work which analyzes the reproductive function in exposed residents will be on doses to genital organs which resulted from exposure to external gamma-radiation and incorporated ^{137}Cs. The doses were estimated by the researchers of the Biophysics laboratory of the Urals Research Center for Radiation (URCRM).

External exposure doses were formed due to gamma-emitting radionuclides (^{137}Cs, ^{95}Zr, ^{95}Nb, ^{106}Ru) present in the effluents contaminating the river water, bottom sediments and flood-plains along the Techa [24]. The basic data used in external exposure dose reconstruction were the following:

- information on total activity, dynamics and radionuclide composition of discharges;
- data from measuring specific activity of bottom deposits;
- results of direct measurements of air exposure dose rates in the high-water basin and residential areas;
- life-style patterns for different age groups of riverside residents, i.e., the estimation of time period spent at different contaminated sites.

It should be pointed out that measurements of exposure dose rates were not conducted until 1951 in the upper reaches of the river, and not until 1952 over the entire course of the river. The reconstruction of gamma-fields for years 1950 and 1951 all over the course of the river was based on data from measuring specific activity of river water, total activity, dynamics and radionuclide composition of the waste discharged. Life styles defined as an average time period spent by residents of riverside villages at sites with different exposure dose rates were calculated by Prof. M.M. Saurov in the 1960s. The major contribution to the dose of external exposure resulted from a stay, even if brief, in the contaminated flood-plain area at the water edge, since on the streets of settlements the gamma-background was 50-150 times lower. It was assumed that, on the average, children and adolescents spent 2 hours, and adults only 1 hour a day at the river. The process of dose accumulation due to external exposure actually stopped after 1956 when the residents of the upper Techa were re-settled, and in the rest of the villages the contaminated flood-plains were fenced off. Annual doses from external exposure for residents of the riverside area assigned to different age groups are presented in Table 1.1.

Table 1.1

Annual external exposure doses in the periods
1950-1951 and 1952-1956 (mGy/yr)

Villages	1950-1951 Children born in 1944-1950	1950-1951 Adolescents born in 1935-1943	1950-1951 Adults born before 1935	1952-1956 Children born in 1944-1950	1952-1956 Adolescents born in 1935-1943	1952-1956 Adults born before 1935
Metlino	410	810	390	63	130	60
Techa-Brod	390	760	360	58	120	54
Assanovo	270	550	260	42	84	40
Nadyrovo	130	250	120	19	39	13
Muslyumovo	17	34	16	4	8	3
Brodokalmak	7	14	7	2	4	2.5
Russkaya Techa	4	8	4	2	4	2
N. Petropav-lovka	4	8	4	2	4	2
Villages in Kurgan Region	3.5	6	3	1.5	3	1.5

Average doses from external exposure as is shown by calculations are a function of the distance along the river from the discharge site. The highest doses of external exposure were received by the residents of Metlino whose average-for-village doses made up 0.50-1.0 Gy/yr. In the lower reaches of the Techa on the territory of the Kurgan Region (150 km from the discharge site) external exposure doses did not exceed 0.01 Gy/yr even in the period of the heaviest discharges (Table 1.2).

Table 1.2

Average doses of external exposure (mGy) for residents of the Techa riverside villages

Villages	Distance from discharge site (km)	External exposure
Metlino	7	1,220
Techa Brod	18	1,130
Assanovo & Nazarovo	33	860
M.Taskino	41	710
Gerassimovka	43	570
Nadyrov Most	48	370
Nadyrovo	50	380
Ibragimovo	54	280
Issayevo	60	190
Subsidiary Farm	65	130
Muslyumovo	78	68
Kurmanovo	88	39
Karpino	96	31
Zamanikha	100	29
Vetroduika	105	26
Brodokalmak	109	28
Osolodka	125	18
Panovo	128	22
Cherepanovo	137	18
Russkaya Techa	138	22
Baklanovo	141	18
N.Petropavlovka	148	21
2-Beloyarka	155	20
Lobanovo	163	20
Anchugovo	170	20
Verkhnyaya Techa	176	20
Skilyagino	180	20
Bougayevo	186	20
Doubassovo	200	20
Bisserovo	202	20
Shutikha	203	20
Progress	207	20
Pershino	212	20
Ganino & Markovo	215	20
Klyuchi	223	20

The rates of ^{137}Cs body intakes were calculated with allowance made for variations in the radionuclide composition of river water with distance from the discharge site. Dose calculations were made using the “average-for-group values” approach. It was assumed that the dynamics of dose accumulation was the same (average-for-group) for all persons of a specific age living in the same specific village in the same specific year. The intakes of radionuclides for the period 1950 through 1959 were taken into account. The contribution of the intake of the first decade to the total dose constituted 99.8%, which is why it was deemed logical to ignore the intake of radionuclides after 1959. The village of Muslyumovo was used as a reference village for estimating the annual intake for the rest of the villages on the river [24] (Table 1.3).

Table 1.3

Coefficients for internal exposure dose re-calculation for different villages *vs* the reference village Muslyumovo

Name of village	Coefficient of re-calculation	Name of village	Coefficient of re-calculation
Metlino	0.76	Cherepanovo	0.42
Techa Brod	0.26	Russkaya Techa	0.38
Assanovo & Nazarovo	0.76	Baklanovo	0.11
M. Taskino	0.73	N. Petropavlovka	0.49
Gerassimovka	0.80	2-Beloyarka	0.54
Nadyrov Most	0.59	Lobanovo	0.38
Nadyrovo	1.04	Anchugovo	0.45
Ibragimovo	1.04	Verkhnyaya Techa	0.50
Issayevo	0.73	Skilyagino	0.71
Subsidiary Farm	0.95	Bougayevo	0.43
Muslyumovo	1.00	Doubassovo	0.26
Kurmanovo	0.62	Bisserovo	0.45
Karpino	0.82	Shutikha	0.12
Zamanikha	0.60	Progress	0.28
Vetroduika	0.76	Pershino	0.24
Brodokalmak	0.21	Ganino&Markovo	0.20
Osolodka	0.60	Klyuchi	0.11
Panovo	0.66	Zatecha	0.29

The doses from incorporated ^{137}Cs were calculated using the age-dependent metabolism model described in the ICRP Publication 56 [27]. The calculations were made using the “average-for-group values” approach. Annual internal doses to gonads for different age groups of the Muslyumovo population in the period 1950-1954 are presented in Table 1.4.

Table 1.4

Annual internal exposure doses to gonads received by Muslyumovo residents assigned to different age cohorts in the period 1950-1954 (mGy/yr)

	Year of Birth

Calendar year						
	1930 and older	1931-1935	1936-1940	1941-1945	1946-1949	1950
1950	25	26	31	24	10	5
1951	20	19	18	12	6	4
1952	10	9	9	9	7	6
1953	4	4	4	3	2	2
1954	1	1	1	1	1	1

Calculations of doses by year was made. The year of termination of follow-up or death were considered to be the cut-off year for dose accumulation.

Table 1.5 demonstrates the average values of doses to gonads calculated for the residents of each of the villages [26].

There is a wide range of variations of average doses to gonads in different settlements: from 21 mSv to 1,270 mSv. It should be noted that though it is difficult to estimate the uncertainty of doses, it is assumed to be significant. This feature can be attributed to the lack of data on gamma-fields for years 1949-1950 (no measurements of gamma-fields were performed at that time), and to the fact that “life style patterns” typical of different age groups have not been identified accurately.

Table 1.5

Average organ-absorbed doses 10 $^{-2}$ Gy (external and internal) for residents of the Techa riverside villages

Village	Population, n	External exposure	Internal exposure	Gonadal dose	Doses to bone surfaces

Metlino	1,242	1,220	50	1,270	2,260
Techa Brod	75	1,130	20	1,150	1,480
Asanovo and Nazarovo	898	860	40	900	1,900
M.Taskino	147	710	40	750	1,680
Gerasimovka	357	570	20	590	1,630
Nadyrov Most	240	370	40	410	1,220
Nadyrovo	184	380	60	440	1,180
Ibragimovo	184	280	60	340	1,800
Isayevo	434	190	40	230	1,700
Podsobnoye Khoz.	487	130	40	170	1,190
Muslyumovo	3,230	68	52	120	1,410
Kurmanovo	1,046	39	36	75	1,430
Karpino	195	31	47	78	880
Zamanikha	338	29	34	63	1,150
Vetroduyika	163	26	47	71	1,060
Brodokalmak	4,102	28	5	33	310
Osolodka	362	18	31	49	830
Panovo	129	22	35	57	910
Cherepanovo	222	18	22	40	590
Russkaya Techa	1,472	22	15	37	530
Baklanovo	480	18	3	21	170
N.Petropavlovka	919	21	22	43	680
2-Beloyarka	386	20	26	46	750
Lobanovo	626	20	17	37	530
Anchugovo	1,093	20	21	41	630
Verkhnyaya Techa	979	20	24	44	700
Skilyagino	492	20	38	58	900
Bugayevo	1,074	20	20	40	600
Dubassovo	703	20	10	30	370
Bisserovo	465	20	21	41	630
Shutikha	1,109	20	2	22	180
Progress	205	20	11	31	400
Pershino	1,143	20	9	29	340
Ganino and Markovo	220	20	7	27	290
Klyuchi	1,309	20	1	21	170
Zatecha	1,135	20	12	32	400

1.1.2 Doses to other organs and fetus

The Table 1.5 presented above shows dose values to bone surfaces too. This parameter should be taken into account in reproductive function evaluation because of the involvement of the hypophysis in the endocrine regulation of the sexual development. Plutonium incorporation in the bone surfaces of the sella turcica which encloses the hypophysis pre-determines the possibility of direct irradiation of the endocrine tissue. The doses to bone surfaces exceed significantly the doses to gonads, but there is a certain parallelism between them.

The radiation exposure which was observed in the Techa riverside villages was of a complex nature. The chronic exposure of the population resulted from:

- external exposure which was going on during the first 6 years, the highest dose rates being observed in the period 1950-1952;
- internal exposure in the period of radionuclide body intakes with water and food-stuffs of local production (late 1949-1956);
- internal exposure due to incorporation in the body of strontium and cesium radionuclides with a long half-excretion period.

In view of the foregoing the analysis of the health status for the offspring should involve not only parental gonadal doses but the factor of antenatal exposure as well, in case gestation coincided with the period of the highest exposure dose rates, i.e., in 1950-1952.

In calculating doses to fetus the dose received by mother due to external exposure and exposure to ^{137}Cs as of the year of pregnancy was made allowance for. According to preliminary data the average dose to fetus was estimated as 38 mSv [28].

1.1.3 Sampling of dose groups for reproductive function evaluation

In order to assess the significance of deviations of this or that parameter *vs* radiation exposure the dose-effec t method was used. We tried to adhere to this principle in sampling study groups among patients with CRS and exposed population on the basis of doses to gonads: <50, 50-99, 100-149, 150-199, 200-299, 400-1,000, >1,000 mSv. However, the analysis of dose-effect dependence for such rare phenomena as neonatal death rate, congenital abnormalities, etc., could only be made if larger (merged) groups were used.

One more approach to radiation effect analysis was to study the reproduction function parameters using separate groups of children in which mother only, father only, or both parents were exposed, i.e. in accordance with the recommendations of the ICRP. In cases of exposure of both parents their gonadal doses were added up.

1.2. Cohorts studied and methods of study

1.2.1 Cohort studied

The goal of the present study is to investigate the reproductive function in patients with the diagnosis of chronic radiation sickness (CRS). In all, 940 exposed residents of the Techa riverside area were diagnosed with CRS. A detailed description of CRS patients (annual dose rates, cumulative doses to the red bone marrow, clinical symptoms of the disease, course and outcomes of CRS) were described in the prior reports [29, 30]. The clinical manifestations of CRS included: hematological syndrome which in some patients makes itself evident as moderate bone marrow hypoplasia, and as decreased counts of leukocytes, neutrophils and thrombocytes in the peripheral blood; CNS affection syndrome; neurological syndrome manifested by asthenization, disturbed vascular regulation, vertebrogenic disorders and, less frequently, by diffuse micro-necrotic changes in the myelinic membranes of the conductors; neuroendocrinal disorders. There were 326 men and 614 women among patients with CRS. They were of different ages by the time the diagnosis of CRS was made: 156 individuals were aged 50 years and older, i.e., they attained the age at which the reproductive function is on the decline. It was thought important to examine subjects of younger ages whose sexual development and sexual maturity coincided with the period of considerable exposure rates. Age and sex distribution of patients with CRS is presented in Table 1.6.

Table 1.6

Age and sex distribution of patients with CRS

Age (yrs) at start of exposure (by 1950)	Men		Women	
	# of cases	%	# of cases	%
31 and older	109	11.6	315	33.5
30-21	49	5.2	123	13.1
20-11	85	9.0	113	12.0
10 and younger	83	8.8	63	6.7

In addressing the epidemiological tasks (analyzing marriage coefficients, assessment of birth rates, etc.) an attempt was made to analyze the effects for the entire CRS cohort. However, this goal was not achieved in full measure, since, as is described in the report [30], some members of the cohort migrated, thus, they were lost to follow-up, due to which data on their marital and family history are not available. The analysis of the clinical parameters (establishment and extinction of the menstrual function, diseases of the reproductive system organs, etc.) was based on a cohort including a representative sample selected among CRS patients.

1.2.2 Comparison groups

One of the key tasks involved in any research of radiation effects is sampling a suitable comparison group. Theoretically, preference should be given to unexposed contingents matching the study cohort in terms age, gender, methods and period of followup. Unfortunately, there does not exist a population group which has been examined over the 45-year period with the same periodicity as patients with CRS.

In view of the foregoing different comparison groups were sampled by us to allow an analysis of different parameters characterizing the reproductive function:

- in a number of cases the parameters studied were compared to those registered before exposure;
- in some sections of the present report the cohort of people who were exposed on the Techa but did not develop CRS is referred to as a comparison group.

The group in question numbers 25,497 subjects. The members of this group are compatible with the CRS cohort in terms of gender, residence history and exposure conditions. However, patients with CRS were slightly different from non-CRS individuals in terms of age; besides, patients with CRS were examined with higher periodicity;

- The comparison group used in analyzing outcomes of labor based on interviewing women consisted of individuals who came to live in the Techa riverside area after 1952, i.e., when radiation conditions had significantly improved; gonadal doses did not exceed 10 mSv for these residents (late-entrants). In subsequent years the late entrants lived in the same conditions as exposed residents, and were followed-up at the URCRM clinic;
- Moreover, some sections describing epidemiological parameters present data on unexposed individuals living in the same administrative districts as exposed persons (regional control).

1.2.3 Research methods

The reproductive system is characterised by multiple levels of functioning. The process of reproduction includes maturation of sex cells, impregnation, intrauterine development of the embryo, birth of the child. The analysis of the reproductive function should, naturally, include the above-listed stages. For this reason, the present study aimed at evaluation of effects of chronic irradiation and development of chronic radiation sickness on the process of reproduction, includes analysis of the following parameters and body functions:

- genital organs morbidity,
- menstrual function ,
- marriage coefficient ,
- incidence of childless marriages and analysis of their causative factors ,
- course of pregnancy ,
- unfavourable outcomes of pregnancy ,
- rate of fecundity ,
- sex ratio for the offspring ,
- health status for neonates ,
- death rate for the offspring.

The next section presents a description of the methods used for analyzing individual parameters listed above.

- *genital organs morbidity*

Morbidity of genital organs, endocrine pathology and toxic effects resulting in impaired maturation and deranged function of sex cells, are the most common causes of infertility.

A number of neuroendocrine glands, other than the genital, influence the process of sex cell maturation: hypothalamic area of the brain, pituitary gland, thyroid, and adrenal gland. Apart from exposure to radiation, infertility may be caused by some occupational toxic factors, immune disorders, endocrine disorders which result in deranged process of ovulation. Secondary infertility may rather frequently be associated with inflammatory processes in the genital glands and sexually transmitted communicable diseases. In view of these features identification of the causes leading to infertility presents a fairly difficult task.

In current clinical surroundings a method of choice used to investigate the causes of infertility is evaluation of the hormonal status, particularly that of estrogens, both total level of estrogen and its fractions, estradiole, estrone, estriole. However, in the 1950s (the period characterized by maximum dose rates) our clinic, whose task it was to follow up patients with CRS, had no appropriate facilities for conducting hormonal studies. We can judge on the adequacy or inadequacy of sex hormone production, and maturation of follicles, indirectly, on the basis of the menstrual cycle follow-up.

Male infertility may result from the following causes: exposure to radiation, chemicals, salts of heavy metals, along with androgen deficiency, chromosomal diseases (Klinefelter's syndrome), diseases of the testes (chryptorchidism, orchitis), disturbed function of the prostatic gland (prostatitis), sexual act derangement (impotence), chronic general somatic diseases: diseases of the respiratory organs (bronchoectasis), diabetes, hepatic and renal insufficiency. The method of choice used to identify the causes of male infertility is to study the sperm. Unfortunately, such investigations were not performed in the 1950s-1960s at the clinic where CRS patients were observed.

The study of genito-urinary system morbidity was based on information resulting from multiple years of follow-up conducted by the clinical department of the Urals Research Center for Radiation Medicine for people exposed on the Techa, including those who were diagnosed with chronic radiation sickness. On the basis of follow-up data and diagnoses established as a result of examinations a computer file <DIAGNOSIS> was created in the URCRM's data base. The file <DIAGNOSIS> contains 167,731 entries on diagnoses, including data on 126,457 cases of diseases diagnosed over the 40-year follow-up in residents exposed on the Techa. Cases of genito-urinary system disorders (ICD Class 10) were selected among patients with CRS [31].

■ *menstrual function*

We can form an opinion on the adequacy of sex hormones production and follicle maturation on the basis of indirect evidence resulting from studies of the menstrual cycle. In an effort to collect data on gynecological history, including that on menstrual cycle, a special questionnaire was developed. In the period 1985-1989 787 exposed women were interviewed using the questionnaire, including 126 women with CRS. The information on age at menarche and that at menopause, duration of the menstrual cycle, pains and quantity of discharge, was collected and recorded by the gynecologists.

■ *course and outcomes of pregnancies*

Information on the course of pregnancies and labor were collected from different sources:

1) labor histories: registration form No 96 approved by the USSR's Health Ministry. 1,219 labor histories were received from:

a/ maternity department of the village hospital in Muslyumovo;

b/ maternity home of the central district hospital hospital in Kunashak.

Labor histories were collected for the period 1956-1973. The maternity department of the Muslyumovo hospital mainly admitted exposed women from the village of Muslyumovo. Kunashak maternity home admitted exposed women from the village of Kurmanovo and mostly unexposed women from the villages Kunashak, Borissovo, Sultanovo, Nugumanovo, Surakovo, Sarino, Aminyevo, Maly Kunashak. On the whole, labor histories are available for 662 exposed women (including 39 women diagnosed with CRS) and 557 unexposed women.

Labor histories contain entries on the current pregnancy, course of pregnancy, as well as information obtained by interviewing women about the prior pregnancies; in all, labor histories contain 6,600 entries on prior and current pregnancies.

2) Interviewing 872 exposed women, including 129 women with diagnosed CRS, conducted by gynecologists in the period 1985-1989. Interviews were conducted on the basis of specifically designed questionnaire containing questions on gynecological history, sexual relations, course and outcomes of pregnancy and labor. The questionnaires completed by women contain information on 6,996 pregnancies which occurred both among exposed women from the Techa cohort and women who settled in the Techa area after 1952 (internal control).

Labor histories and questionnaires provided information on the outcomes of 13,500 pregnancies, of which 12,000 occurred in exposed and 1,500 unexposed (control) women. There were, also, 55 entries on the course of pregnancies in control (unexposed) women whose husbands were exposed. Because of the small size of the latter group it was deemed pointless to analyze these data.

As a result of linking the information from the two above-indicated sources it became evident that information on 96 women was available both in labor histories and responses to questionnaires.

Both of the methods used for collecting information have their advantages and disadvantages. The records contained in labor histories are closer in terms of time to the start of radiation exposure, more significant for analyses of outcomes of pregnancy and labor, and more reliable in terms of registration of unfavorable pregnancy outcomes. This information allows to establish a control (unexposed) group. However, all this information relates to women who were exposed in the villages of Muslyumovo and Kurmanovo, and who actually received equal cumulative doses to gonads. This feature does not allow to elicit dose-dependence of the effect studied.

The interview method implies analysis of pregnancy outcomes for women from different populated areas for a long period of time which allows to trace dose-dependence of the parameters analyzed. However, it cannot be denied that a considerable proportion of relevant information is misrepresented in the process of interviewing the women about the past events. It should be taken into account that the use of the interview method may result in a certain number of both false-positive and false-negative diagnoses, though the method has the right to existence [33].

In view of the foregoing the analysis of a number of parameters, such as pregnancy complications, course of labor and pathological labor, was carried out in this study on the basis of only case histories. Data of interviews were used to estimate the number of abortions.

■ *health status in neonates*

Information on health status of newborn children was obtained from the following sources:

1/ newborn's development history (registration form N 97 introduced by the USSR's Health Ministry). As a rule, the newborn's development histories which were attached to labor histories were obtained from the maternity homes of Muslyumovo and Kunashak, and abstracted. The newborns' development histories contained information on hereditary factors both on maternal and paternal side, labor traumas, developmental defects and deformities, diseases of newborns, immaturity, body weight and length, head circumference, neonate's health status diary covering the period spent at the maternity home. This source provided information on 3,360 newborns, including 128 children born to women diagnosed with CRS.

2/ interviews of exposed women conducted by gynecologists and focusing on the health status of the newborn children: date of birth, gender, weight, body length, circumference of head and chest, single or multiple pregnancy, live- or stillborn, early neonatal death, the child's development during the first year of life. On the basis of the interview data health status of 1,982 newborns was studied, including that of 238 children born to women with CRS.

3/ birth certificates which were retrieved from the Civil Registrar's Office (ZAGS) archives and which contain entries on stillbirth.

■ *marriage coefficient*

Information on marriages for exposed persons with CRS and on birth of children in the families were retrieved from the URCRM's computerized database "MAN" which contains medical and dosimetric data on exposed persons and their offspring. The database includes a "family units" file which was created as a result of fusion of the exposed cohort and offspring file on the basis of family connections. A family identification number unifying the system numbers of spouses and their children was introduced. A Techa cohort member may appear among members of two families: to one of them such person is a child, and to the second a spouse. Such structure of the database allows to promptly identify married or unmarried persons, those with or without children.

The offspring file included in the URCRM's database allows to identify the number of children representing the offspring of persons with CRS, and calculate the fertility and sex ratio for the offspring.

■ *death rate among offspring*

Death rate among the offspring was estimated on the basis of death certificates obtained from the regional ZAGS archives. According to regulations death certificates should be stored for 75 years. It is a document used for registering a death case which contains information on the person's last name, first name, patronymic, birth date, birth place, occupation, death date, death place, cause of death. Death certificates are copied, and the death causes are coded according to ICD-9, complete information from death certificates being transferred to the computer file of the URCRM's database. Death cases among the offspring of exposed parents, parents with CRS, in particular, were picked out from the computer file.

Chapter 2. Analysis of Genitourinary System Disorders

The DIAGNOSIS file for pathological conditions of all types in the URCRM Data Base includes data on 126,457 cases of diseases diagnosed over the 40-year period of followup among residents of the Techa riverside villages. Of this number

22,732 cases were registered among 940 patients with CRS, and 103,725 among 12,437 followed-up exposed residents without CRS.

Diseases of the genitourinary system are assigned to class 10 of the ICD 9 which includes both disorders of the urinary and genital systems.

Information on the fraction of genitourinary system disorders for CRS patients and exposed persons without CRS are presented in Table 2.1.

Table 2.1

Incidence of genitourinary system disorders among exposed persons with and without CRS

Characteristics	CRS patients	Exposed persons
Total subjects	940	12,437
Total registered disease cases	22,732	103,725
Total ICD 9 Class 10 diseases	1,113	5,223
% of Class 10 diseases among others	4.90	5.04
Incidence of Class 10 diseases per 1,000 persons	1,184.0	420.0

It can be seen that 1,113 cases of genitourinary tract disorders were diagnosed among patients with CRS and 5,223 cases occurred among exposed residents without CRS. The calculation of disease rate per 1,000 followed-up members of these groups yielded significantly different coefficients: the disease rate was significantly higher for patients with CRS. However, there is hardly any grounds to suggest dependence of this difference on radiation exposure and CRS. As was stated above (Chapter 1), patients with CRS were examined more regularly, they were summoned to the clinic to be examined and treated, a feature which, in all evidence, may have resulted in higher values of Class 10 disease rate observed at our clinic among CRS patients. The latter supposition can be confirmed by the following two facts. The first one is an equal contribution, about 5%, of genitourinary pathology to total diseases observed in both compared groups: patients with CRS and exposed individuals without CRS. The second circumstance which should be taken into account is that while 100% of patients with CRS underwent medical examinations, only 12,500 out of 25,000 (50%) exposed persons were examined. The foregoing implies that the exposed cohort cannot serve as an adequate control for the CRS cohort in a study aimed at analyzing disease incidence.

The structure of genitourinary diseases for male and female patients with CRS is presented in Tables 2.2 and 2.3.

Table 2.2

Structure of genitourinary pathology for male patients with CRS

Genitourinary pathology,	Number	Incidence/1,000

ICD-codes	of cases	
Nephritis, nephrosis (580-589)	2	6.13
Infections and calculi of the urinary system (590-599)	38	116.56
Hyperplasia of the prostate (600)	42	128.83
Other disorders of the prostate (601-602)	6	18.40
Orchitis and epidydymitis (603-604)	8	24.54
Infertility (606)	0	0
Other disorders of male genital organs (607-608)	0	0
Total	96	294.48

For men the main proportion of genitourinary diseases was represented by inflammatory disorders of the urinary tract, and the latter by urinary tract infections. In all, 56 cases of genital system diseases proper were registered, 42 being diagnosed as prostate hypertrophy in elderly men. There were 14 cases of diseases which can potentially be of interest in male infertility studies. Among them there were 6 cases of prostatitis and 8 cases of epidydymitis. The incidence of orchitis and epidydymitis occurring at different gonandal doses is shown in Fig.2.1. It can be observed that the rate of these inflammatory pathology is independent of dose.

No cases of infertility as a clinical entity (ICD rubric 606, Class 10) was registered among the studied population.

Table 2.3

Structure of genitourinary pathology for female patients with CRS

Diseases of genitourinary system, ICD- codes	Number of cases	Incidence/1,000
Nephritis, nephrosis (580-589)	15	24.43
Infections and calculi of the urinary system		

(590-599)	172	280.13
Breast pathology (610-611)	6	9.77
Inflammatory disease, endometriosis (614-619)	348	566.77
Noninflammatory disorders (620-625)	226	368.08
Disorders of menstruation, menopausa (626-627)	205	333.88
Infertility (628)	45	73.29
Other disorders of female genital organs (629)	0	0
Total	1,017	1,656.35

There were 187 cases of urinary system disorders and 824 cases of genital system disorders diagnosed in women with CRS. The rate of genital system diseases calculated per 1,000 was estimated to be 1,342.0 which implies that, on the average, each woman diagnosed with CRS developed more than one disease (1.34, more precisely) of the genital organs over the 40-year period of follow-up. The most significant proportion of the total pathology of female sex organs consisted of inflammatory processes: colpitis, cervicitis, endometritis, salpingo-oophoritis. These processes could be initiated by different kinds of bacteria, Candida fungi, trichomonade. Endometritis is most frequently associated with abortions or diagnostic curettage of the uterus [34]. Factors contributing to causation of inflammatory diseases of the genital organs in women residents of the Techa villages included inadequate living conditions, absence of sewerage, use of outdoor toilets in any weather (in winter time temperatures reached 20-30 degrees below 0), as well as numerous abortions.

Non-inflammatory processes are chiefly represented by erosion of the cervix uteri, i.e., desquamation of the stratified squamous epithelium of the vaginal part of the cervix uteri. An important role in the etiology of this process is played by inflammatory cervicitis and, possibly, by a disturbed steroid hormone balance. Dysplasia accompanying the erosion process is considered to be a pre-cancer condition.

Data characterizing the dose dependence of inflammatory (ICD Class 10, Rubrics 614-619) and non-inflammatory (ICD Class 10, Rubrics 620-625) processes going on in the genital organs of female patients with CRS are cited in Table 2.4 and Fig. 2.2. No clear-cut dependence on gonadal dose has been established for this pathology.

Table 2.4

Analysis of dose dependence for inflammatory and non-inflammatory disorders of the female genital system in patients with CRS

Dose to gonads, mSv	Inflammatory disorders		Non-inflammatory disorders	
	cases	coefficient $\times 10^{-3}$	cases	coefficient $\times 10^{-3}$

37	92	398 (321.0-488.3)	36	156 (109.1-215.6)
73	61	415 (317.5-534.9)	55	374 (281.7-487.1)
161	103	954 (778.2-157.8)	70	648 (504.9-818.5)
1,044	92	719 (578.6-881.8)	65	508 (392.0-649.9)

The diagnosis of infertility was made in 45 cases which accounts for rate value of 73.3 calculated per 1,000 female patients with CRS. The question of whether these cases represent primary or secondary infertility will be addressed below in the sections discussing the data on infertile marriages and numbers of children born. According to the Russian statistics, infertility rate is a highly variable characteristics, liable to locality- and year-specific changes. It is indicated that the fraction of women with primary and secondary infertility constitutes up to 20%.

The data obtained by analyzing dose dependence for women with CRS are presented below (Fig.2.3a). The infertility coefficient proved to be slightly higher for groups with medium gonadal doses 73 - 161 mSv.

Among the 205 cases of diseases associated with menstrual dysfunction diagnosed in women with CRS there were the following: dysfunctional uterine bleeding in women of reproductive age, pathological conditions in the premenstrual period, climacteric syndrome, etc. The menstrual syndrome will be discussed in detail in the next section. Fig.2.3b shows data on the incidence of menstrual disorders at different gonadal doses. This kind of pathology was found to be independent of dose in women with CRS.

Chapter 3. Menstrual Function

Menstrual function was evaluated for 126 female patients with CRS. Of this number there were 42 patients whose age at the onset of exposure was 31 and older (13% of the total women with CRS of the same age), 29 aged 30-21 (23.6%), 38 aged 20-11 (33.6%), and 17 whose age was 10 years and younger (27%). The results of the study were compared to the data on the menstrual function for 661 women who were exposed on the Techa but did not develop CRS. The second comparison group consisted of unexposed women residents of the same administrative districts as exposed women. The members of latter control group were questioned and examined by the gynecologists N. Saushkina, N. Kolbina and L. Dmitrieva, T.Shumakova [35, 36]. The data on age at menarche and age at menopause, duration of menstrual cycle, menstrual pains and quantity of menstrual blood, were recorded by gynecologists on the basis of interviews and questionnaires.

Data on age at menarche for members of different age groups are listed in Table 3.1.

Table 3.1

Age at menarche and incidence of menstrual function disorders

Groups of studied	Number of persons studied	Mean age at menarche	Incidence (%) of delayed menarche (17 yrs and more)	Incidence of hypo-menorrhea (%)	Incidence of hyper-menorrhea (%)
Women with CRS born in: - 1919 and earlier	42	15.88	30.9	2.4	9.5
- 1920-1929	29	15.79	27.6	6.9	37.9
- 1930-1939	38	15.18	26.3	2.6	15.8
- 1940 and later	17	15.06	23.5	11.8	11.8
Exposed women without CRS born in: - 1940 and later	233	14.25	6.0	2.02	19.4

It follows from the data cited in Table 3.1 that there is a clear-cut decrease in age at menarche depending on year of birth. Fig. 3.1 shows it even more clearly. While the mean age at menarche for women born in 1919 and earlier, whose menarche started before the radiation exposure, made up 15.9, the respective value for women born after 1919 was decreasing: 15.8, 15.2, 15.1. In our opinion, this dependence cannot be attributed to radiation exposure. Evidently, the factor of gradually improving life conditions in the post-war period along with growth acceleration processes became manifest in Russia after the 1960s. The same tendency is reflected in the incidence of cases with late age at menarche.

Of special interest are the results obtained by examining a group of women who were under 11 years by the time exposure started. The members of this group born in 1940 and later were exposed to a number of unfavourable factors, including: a/ their childhood years coincided with world war 2 and the hardships of the early post-war period; b/ exposure to radiation and accumulation of the gonadal dose fell on their childhood; c/ they developed CRS. One of the signs which served as a basis for establishing the diagnosis of CRS in some of the patients was infantilism, i.e., retarded and insufficient sexual development. As is indicated in publication [29], in 4 cases out of 940 the key reasons for diagnosis of CRS was the presence of symptoms of endocrine disorders manifested most clearly at the pubertate age among patients exposed in childhood. The disorders were mainly defined as hypoplasia of the genital apparatus.

The mean age at menarche was 15.06 years for CRS patients born in 1940 and later. This value is characterized by a significant uncertainty because of a small number of observations, but this mean age at menarche is slightly higher than that (14.25 years) for women of matched ages who were exposed but did not develop CRS (Fig. 3.2). The differences in age at menarche between the two groups compared are statistically insignificant because of a small number of CRS patients studied. Works published in the 1980s-1990s specified the mean age of 13 years as the age of menarche [34].

It should be kept in view when comparing the proportion of women with delayed menarche (17 and more years) that among 17 studied patients with CRS there were 4 such cases (23.5%), and only 6% of similar cases were identified among exposed non-CRS women of the same age. According to the data of two reports prepared by the gynecologists [35, 36], who in addition to exposed women examined also unexposed control groups numbering 25 and 48 persons, delayed menarche was noted among unexposed women in 0% - 5.4% of cases.

Disturbance of the menstrual cycle represented by hypermenorrhea or algodysmenorrhea was most frequently observed among CRS patients born in 1920-1929. Hypermenorrhea was registered with similar frequency among patients with CRS born in 1940 and later as among women of the same age without CRS. As far as the incidence of algodysmenorrhea is concerned, patients with CRS developed it in 11.8% of cases whereas among the comparison group the condition was observed less frequently - in 2% of cases.

According to literature sources [34], the average age for menopause, the last menstruation, is 50.8 years. Table 3.2 presents data on mean menopausal age for CRS patients and for exposed women of the same age without CRS.

Table 3.2

Mean age at menopause

Groups studied	Number of persons examined	Mean menopausal age
Women with CRS born in: - 1919 and earlier	34	48.0
- 1920-1929	25	48.3
- 1930-1939	23	49.0
Exposed women without CRS born in: - 1919 and earlier	66	48.4
- 1920-1929	164	48.0
- 1930-1939	198	47.7

For women included in our study the age at menopause proved to be lower than that cited in the publication under reference [34], namely, for different age groups from 49.0 to 47.7 years. It can be noted that in patients with CRS the menstrual cycle did not terminate earlier than in women of the same age cohort but without CRS. There is no clear-cut dependence between age at menopause and years of birth (Fig. 3.3). It is in this feature that the difference between our results and the data on medical followup of women A-bomb survivors makes itself evident [14]. It has been shown by the Japanese researchers that the age at menopause increases for unexposed women born in 1935-1939 as compared to women born in 1915-1919. However, it is more important to note that in women exposed to acute radiation due to atomic bombardment the menopausal age decreased at exposure dose to ovaries in excess of 1.5-2.0 Gy.

The results of our attempt at analyzing the dependence of age at menopause on dose for women with CRS are presented in Fig.3.4.

Due to the small size of the sample there is a significant uncertainty inherent in age characteristics for all dose groups which accounts for large values of confidence intervals. It should be noted that there is no evidence of dependence of menopausal age on dose accumulated in the ovaries.

Chapter 4. Analysis of Marriage Coefficient

It was of interest to estimate the fraction of married patients with CRS since it allowed to evaluate the reproductive function for exposed individuals, and provided an insight into the psychological problems faced by them. It was shown by a number of Japanese studies that a proportion of A-bomb survivors did not marry because they had developed an inferiority complex and a fear of giving birth to children with congenital deformities. In a number of cases in order to get married Japanese survivors had to conceal the fact of their having been present in Hiroshima or Nagasaki during the atomic blast.

The situation observed in the villages on the Techa was basically different. The radiation exposure was protracted, chronic, and the main point is that the information on radiation exposure was concealed from the population. It was not until 1989 with the advent of ¨glasnost¨ (openness) in the USSR, i.e., 40 years later, that the residents were actually told that they had been exposed to radiation. The population of several villages was evacuated from the Techa riverside area during the period 1953-1961. The reason for the evacuations was kept secret from the residents, and they were worrying as they were unable to perceive what was behind it.

The number CRS patients who entered into marriage was estimated on the basis of data obtained by interviewing the members of the cohort. The results of the interviews were entered into a questionnaire referred to as "family history" which was designed for this specific aim. The questionnaire which contained questions on the patients' parents, siblings, spouses and children, including birth dates and residences for all of them, served as the basis for developing relevant computer files in the URCRM Data Base. Thus, our information on marriages was based on the interviews, it was not derived from official documents certifying the fact of marriage. As a consequence, the marriage coefficients determined by the National Statistics and those calculated in our study may differ. The marriage coefficient determined by our studies should be higher since it reflects the "biological" rather than legal phenomenon.

It should also be taken into consideration that about a quarter of the followed-up population were Tartars and Bashkirs by nationality and Moslems by religion. The Islamic creed permits monogamy which was prohibited by law.

The data on family histories for residents of the Techa villages inside Chelyabinsk Region have been collected, questionnaires have been filled out and made into computer files. This kind of work has not yet been completed for residents of the Techa riverside in Kurgan Region. Of the total of 940 CRS cases 787 occurred in Chelyabinsk Region. It should be noted that we were only able to analyze 754 cases since we failed to collect family history information on 33 persons who were lost to follow-up in the early period. The results of the study are displayed in Table 4.1.

Table 4.1

Marriage coefficient for patients with CRS

Cohorts	Men	Women	Total
Exposed on the Techa inside Chelyabinsk Region	287	500	787
Family histories available	265	489	754
Married	262	482	744
Marriage coefficient (%)	98.9	98.6	98.7

Thus, it can be seen that 3 men and 7 women did not enter into marriage after they attained the marital age. These cases were analyzed individually. Two of the men who were born in 1938 and 1946 and whose CRS was diagnosed in 1957 died at the age of 19 and 21. Those were cases of sudden death from an unidentified cause. The third man born in 1936 was diagnosed with CRS in 1953, and in 1966 he was noted to have recovered from his disease. Later on, he was followed up by the URCRM clinical staff until 1974, but he never gave any reasons for his being unmarried.

Of the seven unmarried women with CRS four died at the age 19-27 from acute leukemia, cysticercosis of the brain, cerebrospinal sclerosis, and suicide. One woman born in 1932 has been an invalid since the age of 7 because of amputation of both legs and left forearm after a railway disaster. The two remaining women, twins born in 1944, were diagnosed with infantilism which is evidently the cause of their being unmarried. The past history of these two women is presented in [29].

The marriage coefficient for patients with CRS is, on the whole, sufficiently high: 98.7%. It is quite compatible with the values cited for control in reference [37], namely, 96.5%. The USSR’s national statistics for 1987 based on information on officially registered marriages shows lower marriage coefficients: 81.9%-82.6%.

Chapter 5. Birth of Children to Families of CRS Patients

The information on birth of children based on family history is available for 721 patients with CRS. As was indicated above, 744 members of the cohort married. However, 23 individuals left the locality (in the catchment area), and no information on the birth of children in their families is available.

The age composition of the study group is given in Table 5.1.

Table 5.1

Age at start of exposure for the CRS cohort

Age at start of exposure	Men	Women	Total
≤ 20 years, born in 1930 and later	121	133	254
21-44 years, born in 1931-1906	101	249	350
≥ 45 years, born in 1905 and earlier	32	85	117

It can be seen that among patients with CRS 117 individuals were aged 45 and older by the time the exposure started. At this age the function of the reproductive system ceases. Of great significance for birth rate analysis were the remaining two age groups numbering 604 subjects who were under 45 by 1950. Their childbirth age coincided with the period of exposure to external radiation and incorporated radionuclides. The rate of childless marriages among the three age groups defined above is shown in Table 5.2.

Table 5.2

Rate of childless marriages

Age at start of Exposure	Men		Women		Total	
	cases	%	cases	%	Cases	%
≤ 20 years, born in 1930 and later	2	1.65	8	6.01	10	3.94
21-44 years, born in 1931-1906	6	5.94	6	2.41	12	3.43
≥ 45 years, born in 1905 and earlier	0	0	4	4.71	4	3.42

In all, 26 childless marriages were identified among 721 individuals studied. The proportion of childless families among married men and women diagnosed with CRS is about the same: 3.15% for men and 3.85% for women. A comparison of the percentage of childless families before the exposure (3.64%) with that observed after the start of exposure (3.42), demonstrated that there had been no increase in the rate of childless marriages after 1950.

The causes why a number of marriages were childless remain unclear. The results of reproductive function evaluation and birth coefficient estimation, as well as the influence exerted on them by anthropogenic factors, are difficult to obtain due to the practice of family planning established during the recent decade. In the 1940s-1950s contraceptives were used less frequently, and abortions were banned. However, the likelihood that some families preferred not to have children cannot be ruled out.

There were no children in the families of 8 married men with CRS. Two of them married twice, and one married 3 times, but all of his marriages proved childless. Another man was evidently exposed to occupational, in addition to environmental radiation on the Techa, because he had worked as an X-ray technician since 1953. As was indicated above data on sperm studies for these individuals are unavailable.

Fourteen of the women with CRS were without children. One of them, a young woman, died soon after she was married. The cause of death was active rheumatic process, combined with mitral valve defect and circulatory insufficiency. Another childless woman born in 1905 suffered from a severe general somatic disease - chronic hepatitis associated with alcoholism. Primary infertility was diagnosed by the gynecologists in three patients with CRS on the basis of diencephalic affections, infantile uterus, late menarche. Two other patients were operated on for polycystosis of the ovaries. Chronic inflammatory processes of genital organs (adnexitis, perimetritis, etc.) resulting from aborted first pregnancy, were a likely cause of infertility in four other women. One woman was operated on for ectopic pregnancy following which no pregnancy occurred. No information is available on the causes of childless status for the remaining 2 CRS patients. Thus, the hypothetic causes of childless marriages among patients with CRS are as follows (Table 5.3):

Table 5.3

Probable causes of childless families among women with CRS

Diseases	Number of cases	% of childless marriages
Hormonal disorders	5	27.8
Chronic inflammatory processes of genital organs	5	27.8
Severe extragenital affections	2	11.1

Of considerable interest would be to analyze the rate of childless marriages *versus* doses to gonads. This kind of analysis was conducted for patients who were under 45 years (604 individuals) at the time exposure started (Table 5.4).

Table 5.4

The rate of childless families by gonadal doses

Dose to gonads, mSv	Childless families	Families with children	% of childless marriages
< 50	3	123	2.38
50 - 99	4	170	2.30
100 - 399	8	160	4.76
≥ 400	7	129	5.15

It can be noted that the percentage of childless marriages increases with gonadal dose.

Table 5.4 takes into account the gonadal dose of only one of the spouses. However, both spouses were exposed in two-thirds of the marriages, and only in one-third of the cases either husband or wife were exposed. There are 5 cases for which information on whether or not the spouse of the CRS patient was exposed is missing. Table 5.5 lists data on families with and without children for 577 patients with CRS as a function of exposure of one or both spouses.

Table 5.5

Families with and without children vs exposure of one or both spouses

Group	Families with children	Families without children
Both spouses exposed	404	18 (4.26%)
Only CRS patient exposed, his/her spouse unexposed	173	4 (2.26%)

In case both spouses are exposed, the rate of childless marriages increases about 2-fold, the difference, however, is statistically insignificant. It should be noted that among the 79 families with both spouses diagnosed with CRS there were two childless families (2.53%).

A more correct approach to dose-dependence analysis for childless marriages would be to estimate gonadal doses by adding together doses received by both parents (Table 5.6).

There was a slight increase in the rate of childless marriages with dose to gonads: from 2.9% at doses below 100 mSv to 7.6% at average doses for group of 2133 mSv. Dose dependence is presented in Fig.5.1.

By approximating the dose-dependence for childless marriages using linear regression, the proportion of childless marriages constituting 3.46% is obtained at zero dose, and the coefficient at dose is equal to 2.3 in case the dose calculated per 1 Sv.

Table 5.6

The rate of childless marriages at different aggregate doses received by both spouses

Ranges of doses to gonads for groups, mSv	Families with children	Families without children	Rate of childless marriages, (%)
< 100	100	3	2.91
100 - 199	107	3	2.73
200 - 399	101	4	3.81
400 - 999	35	3	7.89
> = 1000	61	5	7.57

Chapter 6. Course and Outcomes of Pregnancy

It is known that acceleration of mutational process is one of the key effects of ionizing radiation. However, genetic monitoring of human populations for effects of environmental pollution, radiation contamination, in particular, is an extremely complicated task. No data on rates of spontaneous mutational process are available. No adequately developed methodology for assessment of gene mutations existed in Russia. For this reason we had to apply the phenotypical approach to the assessment of the mutagenic effect of radiation, based on the analysis of antenatal fetus loss and congenital developmental defects. This chapter will present the analysis of spontaneous abortions and labor complications which may have been induced by chronic radiation exposure in the Techa riverside villages.

6.1 Medical and criminal abortions

Pregnancies which resulted in medical or criminal abortions were analyzed on the basis of both labor histories and interviewing women. Table 6.1 given below shows only the pregnancies that occurred after the onset of radiation exposure , i.e., after 1949. Labor histories contain 3,772 entries on such pregnancies.

Table 6.1

Data on pregnancies and abortions based on labor histories

Parameters	Women with CRS	Women exposed	Both spouses exposed	Both parents unexposed (control)
Total women followed-up	39	90	533	557
Total pregnancies	154	201	1,894	1,523
Medical abortion	8	13	170	92
Criminal abortions	6	1	3	1
Spontaneous abortions	12	12	56	35
Ectopic pregnancies	0	1	2	1

Information on abortions and the outcomes of the prior pregnancies was based on labor histories taken on the basis of questioning women on their gynecologic and obstetric anamnesis as well as. According to the information based on labor history only a small proportion of pregnancies ended in medical and criminal abortions made, namely, 294 or 7.8%. Information on the incidence of abortions obtained by interviewing women is listed in Table 6.2.

Table 6.2

Pregnancies and abortions based on interviews

Parameters	Women with CRS	Exposed women	Both parents exposed
Total followed-up women	129	286	457
Total pregnancies	1,173	2,036	3,787
Number of pregnancies per 1 woman	9.1	7.1	8.3
Medical abortions	400	1,195	2,025

The analysis of interviews conducted by gynecologists in 1985-1989 showed that abortions made up a much larger proportion of all pregnancies. Only a small percentage of abortions, 0.9% for unexposed cohort, were performed on the basis of therapeutic indications. The rest of the abortions (medical or criminal) were performed according to the wish of the women themselves.

The unified information on the incidence of abortions 9 (according to 2 sources: labor history and interviews) is presented in Table 6.3.

Table 6.3

Summarized information on pregnancies and abortions based on labor histories and interviews

Parameters	Women with CRS	Exposed women	Both spouses exposed	Both spouses unexposed (control)
Total followed-up women	168	376	990	557
Total pregnancies	1,327	2,237	5,681	1,523
Medical abortions	408	1,208	2,195	92
Criminal abortions	25	26	87	1
Spontaneous abortions	39	96	153	35

The data presented here allow to study the outcomes of 6-8 pregnancies which occurred, on the average, in each of the exposed women, and 2.7 pregnancies which were registered in each of the unexposed women (control). It can be seen that those of the followed-up women who did not want to have children hardly used any contraceptives, and the fraction of abortions is very high in relation to the total pregnancies. The number of therapeutic and criminal abortions per 100 labors made up 70-136 for exposed persons, and 51 for women with CRS. These differences can be explained by different mean ages of the women interviewed. The mean age of CRS patients was significantly older, and their reproductive function activity fell mostly on the period when abortions were prohibited. This accounts for a higher incidence (about 60%) of criminal abortions among patients with CRS. In view of the high significance of the data on the incidence of spontaneous (self-induced) abortions for analysis of a potential mutagenic effect of radiation, this issue was discussed in a separate section of the report.

6.2 Spontaneous abortions

The rate of intrauterine fetal loss is an important issues of radiation genetics. One of the components of fetal loss is self-induced or spontaneous abortions. From the point of view of a number of researchers it is expedient to analyze the incidence of spontaneous abortions which allows to register the intensity of the mutational process, since it is assumed by them that about 50% of spontaneous abortions are caused by genetic factors [5]. At the same time, it should be noted that the incidence of spontaneous abortions, according to published data, is highly variable, ranging from 4-5 to 50-60 per 100 pregnant women [32]. According to medical records containing entries on spontaneous abortions, which commonly occur late in the gestation period, their rate accounts for 3-6% of total pregnancies [5], which is evidently lower than the actual rate of spontaneous abortions. Abortions developing at an early stage of pregnancy when the woman is still unaware of the pregnancy, are regarded by her as irregularity of menses and are not registered at medical institutions [32].

According to the data derived from labor histories (Table 6.1), the incidence of spontaneous abortions among exposed women is, on the whole, somewhat higher (3.56%) than among controls (2.30%), however, these differences are statistically insignificant ($p>0.05$). No increase in the incidence of spontaneous abortions was noted for cases with both parents exposed, compared to cases with only mother exposed. The proportion of spontaneous abortions is the highest for women with CRS, but the statistical sample is small.

According to the data of interviews (Table 6.2) the incidence of spontaneous abortions was 2.30% among women with CRS, 4.13% among exposed women, and 2.56% among families with both parents exposed. On the whole, the incidence of spontaneous abortions among total exposed women was 3.0% (95% CI:2.60; 3.43), according to the interview data, thus, it was not statistically different from that based on labor histories. The number of spontaneous abortions calculated per 100 pregnancies is shown in Table 6.4.

Table 6.4

Incidence of spontaneous abortions

Parameter	Women with CRS	Women exposed	Both parents exposed	Both parents unexposed (control)
Total followed-up women	168	376	990	557
Total pregnancies	1,327	2,237	5,681	1,523
Spontaneous abortions	39	96	153	35
Number of spontaneous abortions per 100 pregnancies	2.94	4.29	2.69	2.30

The dependencies determined as a result of analysis of merged data (labor histories and interviews) remain valid when information sources are studied separately, viz., the incidence of spontaneous abortions is somewhat higher for exposed subjects - 3.11% (95% CI: 2.76; 3.81), than for controls – 2.30 (95% CI: 1.60; 3.19), however, no statistically significant differences can be noted ($p<0.05$). The incidence of spontaneous abortions among women with CRS accounted for 2.94% which was not higher than that estimated for exposed women without CRS.

The dependence of the incidence of spontaneous abortions on exposure dose to gonads is shown Fig. 6.1.

Linear approximation of dose dependence allowed to estimate the spontaneous rate as 3.07%, and the estimated coefficient at dose turned out to be positive, though its value (0.08 per 1 Sv) was low.

6.3 Course of pregnancy

The results of analysis of data on the course of pregnancies in Table 6.5.

Other pregnancy complications include threat of pregnancy interruptions, hemorrhage, situs inversus, hydraminon. The most common pregnancy complication was early, late and combined toxicosis. It was indicated in the earlier studies [36] that the incidence of pathologic pregnancy was higher among exposed women compared to controls. The present study allowed to identify essentially more frequent pregnancy complications among women with CRS, viz., 18.75% (95% CI: 12.02; 29.9) compared to the group of unexposed couples – 8.25% (95% CI: 6.8; 9.9).

Table 6.5

The course of pregnancies according to labor history data

Parameters	Women with CRS		Exposed women		Both spouses exposed		Both spouses unexposed (control)	
	cases	%	cases	%	cases	%	cases	%
Number of pregnancies without abortions	128	100	174	100	1,663	100	1,394	100
Number of pregnancies without complications	104	81.3	152	87.3	1,457	87.6	1,279	91.8
Toxicosis	7	5.5	9	5.2	82	4.9	34	2.4
Other complications	17	13.3	13	7.5	124	7.5	81	5.8

6.4 Outcomes of pregnancy

Information on outcomes of pregnancies based on labor history is indicated in Table 6.6.

Table 6.6

Outcomes of pregnancies based on labor histories

Parameters	Women with CRS		Exposed women		Both spouses exposed		Both spouses unexposed (control)	
	cases	%	cases	%	cases	%	cases	%
Number of pregnancies without abortions	128	100	175	100	1,665	100	1,395	100
Ectopic pregnancies	0	0	1	0.6	2	0.1	1	0.1
Labor at term	122	95.3	166	94.8	1,546	92.8	1,319	94.6
Premature labor	1	0.8	7	4.0	82	4.9	49	3.5
Delayed labor	5	3.9	1	0.6	35	2.1	26	1.9

The comparative analysis of outcomes of 128 pregnancies registered among CRS patients, 1,840 pregnancies among exposed women and 1,395 pregnancies among control subjects, did not reveal differences in the incidence of ectopic pregnancies, prolonged pregnancies or premature labors.

6.5 Course of labor

The information on the course of labor could only be derived from labor histories. Besides, only a proportion of medical records contained information sufficient to analyze the nature of labor activity and clear-cut pathology. The information obtained by interviewing women provided no objective basis for estimating the incidence of pathological course of labor activity. Data on the course of labor based on labor history are listed below (Table 6.7).

Table 6.7

Course of labor based on labor histories

Parameters	Women with CRS		Exposed women		Both spouses exposed		Both spouses unexposed (control)	
	cases	%	cases	%	cases	%	cases	%
Number of labors studied	128	100	174	100	1,663	100	1,394	100
Labor pathology, including	31	24.2	26	14.9	225	13.5	177	12.7
- placental pathology	1	0.8	0	0	12	0.7	19	1.4
- umbilical pathology	16	12.5	14	8.0	122	7.3	104	7.5
- other complications, including hemorrhage at labor	14	10.9	9	5.2	87	5.2	44	3.1
- surgical interventions	0	0	3	1.7	4	0.2	10	0.7
Normal labor	97	75.8	148	85.1	1,438	86.5	1,217	87.3

Pathological labor was registered twice as frequently among women with CRS - 24.2% (95% CI: 16.5; 34.3), compared to controls – 12.7% (95% CI: 10.9; 14.7). The differences are statistically significant ($p<0.01$). Labor pathology is commonly manifested by lengthening of the umbilical cord or its entwining about the infant's neck, and by frequent hemorrhages.

Chapter 7. Assessment of Health Status for Neonates

The health status for neonates was assessed on the basis of records made in the neonate's development history. As is indicated above, it became possible to analyze all pregnancy outcomes on the basis of labor histories and newborn's development histories, but only a proportion (1,989 records on newborns) out of 2,996 labors reported by interviewed women were included in the analysis. The respective data are shown in Tables 7.1 and 7.2.

Table 7.1

Health status assessment for neonates based on data from neonate development histories

Parameters	Women with CRS	Exposed women	Both spouses exposed	Both spouses unexposed (control)
Number of women	39	90	533	557
Number of labors	128	174	1,663	1,394
Number of liveborns	128	173	1,672	1,387
Multiple labors	4 - 3.13%	3 -1.72%	35 -2.10%	11 -0.79%
Number of stillborns	4 - 3,03%	4 - 2.26%	26 -1.53%	18 -1.28%
Died within first 7 days of birth	1 - 0,78%	0 - 0%	2 -0.12%	1 -0.07%
Newborns with congenital developmental defects	0 out of 57 0%	0 out of 102 0%	7 out of 830 0.84%	4 out of 605 0.66%

Table 7.2

Newborn health state assessment based on interviews

Parameters	Women with CRS	Women exposed	Both parents exposed
Number of women	129	286	457
Number of labors	284	519	1,183
Number of liveborns	283	519	1,180
Multiple labors	3 -1.06%	5 - 0.96%	6 - 0.51%
Number of stillborns	4 -1.39%	5 - 0.95%	9 - 0.76%
Died within first 7 days of birth	2 - 0.71%	1 - 0.19%	6 - 0.51%

7.1 Birth of twins (multiple pregnancy)

According to literature data the rate of twin birth ranges from 0.4% to 1.6% [6]. Based on interview and labor histories data we were able to analyze 5,327 labors with reference to which reliable information on birth of one or two children was available. The relevant data are shown in Table 7.3.

Table 7.3

Multiple pregnancies

Parameter	Women with CRS	Women exposed	Both parents exposed	Both parents unexposed (control)
Number of labor	412	693	2,846	1,394
Multiple labors	7	8	41	11
Rate of multiple labors, %	1.70	1.15	1.44	0.79

It can be seen that the rate of multiple labor in all groups was found to be within the range of values cited in literature as normal. However, the rate of birth of twins accounted for 1.70% (95% CI: 0.68, 3.50) for women with CRS, 1.42% (95% CI: 1.07; 1.85), i.e., twice higher, for exposed women, and 0.79% (95% CI: 0.39; 1.41). At the same time, the differences observed are statistically insignificant. The dependence of the birth of twins on external exposure doses to parental gonads is shown in Fig. 7.1.

Using the linear approximation equation y=a + bD, the basic level of multiple labor was estimated to be a=1.28%, and the coefficient b = 0.31 at exposure dose 1 Sv.

7.2 Perinatal mortality

7.2.1 Stillborns

The criteria of stillbirth include absence of independent extrauterine breathing at birth and failure to resuscitate the infant using methods of artificial breathing. In accordance to the regulations in force in Russia a stillborn is defined as a fetus born after 28 weeks of gestation with body weight of over 1,000 and body length no less than 35 cm which failed to make a single independent inspiration at birth [6]. Congenital developmental abnormalities of the fetus account for 7,5% in the total structure of causes of stillbirth. Other causes include asphyxia, abnormalities of the placenta and umbilicus, etc. [6].

The coefficient of stillbirth is estimated according to the following formula: ratio of stillborns to the sum of live- and stillborns, multiplied by 100 [38]. However, the values of stillbirth coefficients cited in statistical reviews are calculated per 1,000 live- and stillborns [39, 40]. In 1980 the stillbirth coefficient for the USSR was estimated as 9.11 per 1,000, and for union republics it ranged from 5.15 to 13.81 [39]. For rural localities in 1980-1992 in Russia the rate of stillbirth was 6.5-7.5 per 1,000 liveborns [41].

The data cited in Table 7.1 (above) indicate that stillbirth coefficients registered for maternity homes of Muslyumovo and Kunashak in the period 1956-1973 was essentially higher than that for the USSR in 1980, viz., it accounted for 1.52% (95% CI: 1.13; 1.98) or 15.24 per 1,000. As assessed on the basis of the results of the interviews (Table 7.2) the incidence of stillborns was somewhat lower: 18 cases per 2,000 newborns, or 0.90% (95% CI: 0.53; 1.42). No increase in the incidence of stillbirth resulted from exposure of both parents as compared to exposure of only the mother. A slightly higher percentage of stillbirth was noted for cases with exposed mothers with CRS as compared to the controls, the differences, however, are insignificant.

One more source of information on stillbirth was analyzed, the so-called “birth certificate”. Birth certificates stored at the Chelyabinsk Regional ZAGS archives have been abstracted by the URCRM staff. In all, 4,504 birth certificates pertaining to birth of children to exposed parents 1950-1958 were reviewed. Twenty-seven birth certificates contained entries on stillbirth. Based on this source the stillbirth accounted for 0.6%. It can be assumed that the information on stillbirth contained in labor histories and newborn development histories is more complete compared to that derived from birth certificates. According to legislation in force a stillborn should be registered by the parents at the Regional Registrar’s Office (ZAGS). However, since the procedure was psychologically painful to the parents of the stillborn infant, they refrained from performing those formalities, hence, lack of birth certificates for a proportion of stillborns.

7.2.2 Early neonatal death

Early neonatal death can be defined as death of a neonate during the first week of life. The coefficient of early neonatal mortality is calculated as the ratio of the number of children who died during the first week of life to the number of liveborns, multiplied by 1,000. Congenital developmental abnormalities constitute 14% in the structure of early neonatal death. As a rule, the proportion of neonates who died during the first week of life is 1.5 times lower than the proportion of stillborns [6].

According to official statistics the rate of early neonatal death for 1980 was estimated to be 6.8 for the USSR as a whole, and 3.4 per 1,000 for rural localities [41]. However, it is stated in the same publication that in the USSR the open official statistics underestimated, for political reasons, the rate of infant mortality in general, and above all, the rate of early neonatal death. Highlighting a decrease in child mortality in the USSR the governmental bodies urged the staff of maternity homes to underreport cases of early neonatal death. In order the form an idea of true rates of neonatal death in the soviet period it was suggested to apply adjustment coefficients which allow to estimate the rate value. The calculations are based on regression model of dependence of neonatal death rate on the rate of postnatal death [41].

As can be seen from Table 7.1 only 4 death cases out of 3,360 livebirths were registered at the maternity home: 1 control case, 1 case in a patient with XRS, and 2 cases in families with both parents exposed. In total it yields 1.19 (95% CI: 0.32; 3.05) per 1,000 liveborns. The coefficients of early neonatal death estimated per 1,000 liveborns were 7.81 for women with CRS, 1.20 for families of exposed parents, and 0.72 for controls. Thus, according to information provided by maternity homes which analyzed labor histories and newborn development histories, the rate of stillbirth turned out to be higher, and that of early neonatal death lower than values listed in official sources [39]. It may be due to the fact that obstetricians, afraid of responsibility for cases of early neonatal death, did not register such cases. and to the fact that the criteria according to which a death case should be assigned to antenatal or postnatal death, were not always observed.

According to the interview information (Table 7.2) early neonatal death is higher for total exposed subjects: 9 cases per 1,982 liveborns or 4.54 (95% CI: 2.08; 8.64) per 1,000 liveborns.

7.3 Developmental defects diagnosed at birth

Some authors are of the opinion that the rate of birth of children with developmental defects provides basis for the assessment of intensity of mutational processes [5, 7]. The diseases assigned to the common group of developmental defects or congenital anomalies represent a multi-factor pathology.

At a maternity home it is impossible to diagnose all developmental defects when a child is born. It is assumed that there are about 10 gross developmental defects which can be easily diagnosed at birth (the so called “sentinel” phenotypes [42]): anencephaly, hydrocephaly, microcephaly, bone marrow hernia, congenital aplasia of the extremities, polydactylia, cleft lip and palate, spina bifida, anal atresis, multiple developmental defects. The rate of the above indicated developmental defects may be estimated as 5 cases per 1,000 liveborns [5].

According to the information accessible to us the presence or absence of a developmental defect was registered only in development histories of 1,594 neonates among whom 11 congenital defects were observed. The rate of congenital anomalies calculated per 1,000 newborns made up 6.90; for the exposed it was 7.08 and for controls - 6.61.

The interview method proved ineffective for analyzing developmental defects diagnosed at birth because the interviewed women tend to list developmental defects that were diagnosed for their children at later ages.

7.4 Unfavorable outcomes of pregnancy

Unfavorable outcomes of pregnancy including spontaneous abortions, perinatal death and congenital developmental defects based on the information from labor histories and newborn development histories are presented in Table 7.4.

Table 7.4

Unfavorable outcomes of pregnancies (%) based on labor histories and newborn development histories

Parameter	Women with CRS	Women exposed	Both parents exposed	Both parents unexposed (control)
Spontaneous abortions	7.79	5.97	2.96	2.30
Stillborns	3.03	2.26	1.53	1.28
Early neonatal death rate	0.78	0	0.12	0.07
Congenital developmental defects	0	0	0.84	0.66
Total unfavorable outcomes of pregnancies	11.60	8.23	5.45	4.31

The rate of unfavorable outcomes of pregnancies assessed for exposed persons diagnosed with CRS was higher than for controls, the difference being statistically significant: 11.6% (95% CI: 6.79; 18.58) and 4.31% (95% CI: 3.02; 5.96), respectively.

Unfavorable outcomes of pregnancies including spontaneous abortions and perinatal death based on interviews are presented in Table 7.5.

According to interview data the rate of unfavorable pregnancy outcomes constituted 3.83%-5.26%. Based on both information sources the rate of unfavorable outcomes of pregnancy ranged from 4.31% to 5.71% which is close to the respective values yielded for Hiroshima and Nagasaki populations: 4.80% for the offspring of A-bomb survivors, and 4.64% for controls [7]. It should be noted that according to all information unfavorable pregnancy outcomes are observed with somewhat higher frequency (however, statistically insignificant) than for groups with both parents exposed which actually resulted in a doubled dose. This may be regarded as an indirect evidence of radiation exposure being not an only and, possibly, not a predominant factor governing the rate of unfavorable pregnancy outcomes.

Table 7.5

Unfavorable pregnancy outcomes based on interviews

Parameters	Women with CRS	Women exposed	Both spouses exposed
Spontaneous abortions	2.30	4.12	2.56
Stillborns	1.39	0.95	0.76
Early neonatal death rate	0.71	0.19	0.51
Unfavorable outcomes of pregnancy (total)	4.40	5.26	3.83

As was indicated above, the information contained in labor histories and newborn development histories dates from the time close to the onset of radiation exposure, they are confirmed by documentation, which makes them more reliable and applicable to the analysis of the course of pregnancy and labor, as well as to the identification of unfavorable outcomes of pregnancy. At the same time all data contained in labor histories relate to women exposed in the villages of Muslyumovo and Kurmanovo who had comparable gonadal doses which precluded us from sampling many dose groups for analysis. The results of dose dependence analysis based on a limited number of dose groups are presented in Fig. 7.2.

No differences in the rate of unfavorable pregnancy outcomes were noted within the dose range from 50 to 400 mSv. At the same time, loss of fetus or child was registered less frequently among controls, and significantly more frequently among CRS patients (than among controls). Dose dependence approximation (based on 4 values of gonadal doses) showed a positive, though a very small slope of the approximating curve over the X-axis. At X equal to 0 the rate of unfavorable pregnancy outcomes accounted for 4.58%. The estimated value of coefficient at dose was equal to 0.003 per 1 mSv.

Chapter 8. Anthropometric Characteristics of Newborns

The interest to anthropometric characteristics of children born to exposed parents is mostly motivated by the fact that the incidence of small head size among neonates born to women who were at 10-18 weeks of gestation at the time of acute radiation exposure in Hiroshima and Nagasaki was noted to be increased [19, 20].

The information we have at our disposal includes body weight for 1,565 neonates, body length at birth for 892 neonates. Head circumference was measured with much lesser frequency at the time for which the labor documentation and newborn development histories are available to us. There were in all 510 entries on the head circumpherence measurement. The distribution of newborns by body weight and length was analyzed for three groups:

- children born to parents with CRS;
- children born to exposed parents without CRS ;
- children born to unexposed parents.

The focus of the analysis was on infants born at term (gestational age: 38-42 weeks): twins were excluded from the analysis.

Anthropometric parameters of the newborns are presented in Table 8.1.

Neonates born to CRS patients did not differ in terms of average head circumpherence, body weight and length from those born to exposed people without CRS or controls.

Body weight distribution for the above-indicated groups is shown in Fig. 8.1. The tables to be used for constructing graphs were based on procentiles. It can be observed that in spite of comparable average values, children born to persons with CRS are characterized by a wider scattering, i.e., there is an increased proportion of both children with larger body weights and those with small body weights.

Body length and head circumpherence distribution for neonates born to exposed and control parents is presented in Fig. 8.2 and 8.3. It was impossible to construct a graph describing the distribution of anthropometric parameters for infants born to patients with CRS because of insufficient data. A slight increase was noted in the borderline values of anthropometric parameters for children born to exposed parents. Some authors are of the opinion [10] that the mutagenic effect of the environment may become manifested in "shattered hereditary traits" which may, in particular, be displayed in an increased proportion of borderline values in the distribution of polygenic anthropometric signs. Such is, on the hole, the picture that we observe when we assess the health status of infants born to exposed parents.

Table 8.1

Anthropometric parameters of the newborns

Parameters	Parents with CRS	Exposed Parents	Unexposed parents (control)
Body weight, g,			
- number of followed-up cases	113	860	592
- mean body weight	3,496 ± 562.1	3,406 ± 474.5	3,389 ± 493.0
- maximum body weight	5,300	5,400	5,150
- minimal body weight	2,070	1,870	1,700
Body length, cm			
- number of followed-up cases	43	493	356
- mean body length	52.7 ± 3.7	52.5 ± 3.3	52.1 ± 3.4
- maximum body length	65	62	62
- minimum body length	45	36	36
Head circumpherence, cm			
– number of followed-up cases	14	297	199
- mean head circumpherence	34.7 ± 1.6	34.5 ± 1.9	34.3 ± 1.6
- maximum head circumpherence	38	43	39
- minimum head circumpherence	32	29	29

Chapter 9. Fertility Rate

It was shown in the previous studies focusing on the health status for the offspring of exposed people [23] that:

- temporal trends of birth rate for the population exposed on the Techa are governed by the same dependencies as birth rates observed for the country as a whole, i.e., high birth rates registered in the 1950s and a persistent decrease in the 1960s-1970s when family planning practice became more widely spread;
- higher (1.5-2-fold) birth rates in the 1950s-1960s noted for the Tartar and Bashkir ethnic groups compared to Russians;
- birth rates estimated for the exposed cohort turned out to be not lower than those for the unexposed control.

The focus of the earlier research was on the exposed population of which patients with CRS were a part, none of the previous studies addressed the task of analyzing fertility and birth rate for this specific group. It should be primarily noted that the exposed cohort includes persons born before 1950, the year of the start of radiation exposure. All those born after 1950 should be assigned to the progeny of the exposed parents. Thus, it is only during the first year after the onset of exposure that all age groups are represented in the Techa cohort. In the subsequent years children are no more present, and by 1990 persons aged 40 years are the youngest members of the Techa cohort. The Techa cohort is an aging population, and its birth rates cannot be compared with the respective parameters for control cohorts (e.g., population of Russia) which include persons of all age groups.

It would also be incorrect to make comparisons between birth rates estimated for CRS patients and those for the Techa cohort since the age distribution among CRS population and Techa cohort members turned out to be different.

In view of the foregoing, it was deemed appropriate for the purpose of reproductive function evaluation for patients with CRS to estimate the rate of fertility rather than the birth rate. The fertility rate is calculated as the number of children born within a year to 1,000 women of reproductive age (15-49 years).

In total, 2, 376 children were born to patients with CRS. Of this number 974 were born before the exposure started, and 1,402 after 1949. Numbers of children by year and period of birth, father with CRS, mother with CRS, both parents with CRS, are shown in Table 9.1.

Of 787 patients with CRS exposed in Chelyabinsk Region 500 were women. They gave birth to 1,396 children of which 697 were born before 1950, and 699 were born in the period from 1950 through 1989.

Table 9.1

Birth years for children of patients with CRS exposed in Chelyabinsk Region

Birth years	Father with CRS	Mother with CRS	Both parents with CRS
Before start of radiation (before 1950)	204	697	73
1950-1954	119	222	36
1955-1959	141	179	26
1960-1969	216	224	26
1970-1979	116	69	3
1980-1989	20	5	0
Total	816	1,396	164

The estimated fertility rates are shown in Table 9.2.

Table 9.2

Fertility rates for women with CRS, exposed and control women

Periods of follow-up	Number of women with CRS of reproductive age	Number of children born to women with CRS	Fertility rate for women with CRS	Fertility rate for exposed women	Fertility rate for control women
1950-1954	350	222	126.9 (110.5-144.5)*	139.4	131.6
1955-1959	366	179	97,8 (83.9-113.2)	118.6	107.6
1960-1969	280	224	80.0 (69.7-91.0)	82.3	94.4
1970-1979	199	69	34.7 (27.0-43.2)		
1980-1989	118	5			

Note: 95% confidence intervals are indicated in parentheses

The fertility rate estimated for the period 1969-1970 made up 65.7 for the USSR and 53.4 for the Russian republic, both fertility and birth rate being higher for rural localities than for cities. Judging by the values cited in the above table, the fertility rate estimated for the rural population followed-up by us was not lower than the national rate. On the basis of fertility rates and their 95% confidence intervals a conclusion should be made that the childbirth function was not significantly affected both in women with CRS, exposed women and controls.

Chapter 10. Sex Ratio

Impaired sex ratio observed among the offspring born after to parents exposed to radiation is assumed to be one of potential radiation effects [7, 12].

Normally, newborn boys numerically predominate over newborn girls. The ratio is sufficiently stable and is estimated to be 106 boys to 100 girls, on the average [43, 44]. However, sex ratio is influenced by a number of factors, such as age of parents, unfavorable socio-economic conditions, potential mutagenic effects, radiation exposure, in particular.

It was established as a result of sex ratio analysis for the offspring of A-bomb survivors that there was an increase in the absolute value of sex ratio by more than 4% in case father was exposed, and of the absolute value of sex ratio by more than 1.6% in case mother was exposed [21].

Potential hazardous impacts of radiation as manifested by effects on sex ratio are interpreted on the basis of different assumptions. It was thought that radiation exposure may lead to increased loss of male fetuses, since they are more vulnerable to any adverse effects, and, thus, to predominance of girls over boys among children born to exposed parents. At the same time it was suggested that among the offspring of exposed men there may be a shift of normal sex ratio towards a relative excess of sons in case the exposure caused a considerable number of dominant-lethal mutations which are mostly associated with X-chromosome (while Y-chromosome is almost void). There should be a shift towards a relative increase in the number of daughters among the offspring of exposed women due to the loss of male fetuses which had X-chromosomes with recessive-type injuries. [12].

Table 10.1 shows data on the birth of boys and girls to patients with CRS *vs* exposure of father, mother, or both parents.

Table 10.1

Sex ratio for children born to patients with CRS

Parameters	Father exposed	Mother exposed	Both parents exposed
Children born after onset of exposure			
- number of boys	314	347	46
- number of girls	298	352	45
- number of boys per 100 girls	105,4	98,6	102,2

Before exposure 974 children were born to patients who were later diagnosed with CRS: 492 boys and 482 girls. The estimated sex ratio (number of boys per 100 girls) was 102.1. After exposure 1,402 children were born to parents with CRS: 707 boys and 695 girls. The sex ratio was estimated as 101.7. The analysis of sex ratio *vs* exposure of father, mother or both parents allowed to trace an effect characterized by the expected trend, viz., birth of an increased number of boys to fathers with CRS, and of an increased number of girls to mothers with CRS. It should be noted that deviations from the expected trend, i.e., predominance of boys born to exposed fathers with CRS and predominance of girls born to exposed mothers with CRS, manifested itself during the early years after the onset of exposure, i.e., during the period characterized by the highest dose rates (Table 10.2).

Table 10.2

Sex ratio for children born in different years after the onset of exposure of parents with CRS

Years of birth	Father exposed	Mother exposed	Both parents exposed
1950-1959	150/110 136.4	193/208 92.8	31/31 100.0
1960-1969	101/115 87.8	116/108 107.4	12/14 85.7
1970-1979	51/65 78.5	33/36 91.7	3/0
1980-1989	12/8	5/0	0/0

Note: 1/ the numerator indicates the number of boys, and the denominator the number of girls, 2/ if less than 21 child was born in the time period under study, the sex ration was not calculated.

A comparison between sex ratio estimated for children born to parents with CRS, exposed parents without CRS, and unexposed parents (controls) is given in Table 10.3.

Table 10.3

Sex ratio for children born to CRS patients, Techa cohort members, and controls

Exposure to ionizing radiation	Exposed persons with CRS	Exposed persons without CRS
Father exposed	314/298 105.4	4,145/4,105 103.9 ± 2.86
Exposed mother	347/352 98.6	1,513/1,441 105.0 ±2.73
Both parents exposed	46/45 102.2	1,333/1,283 101.0 ± 1.57
Unexposed parents (control)		26,298/25,389 103.6 ± 0.64

Note: the numerator represents the number of boys, the denominator - the number of girls

The control group comprises data on 51,687 children born between 1950 and 1974 to unexposed parents who lived in the same administrative districts as the exposed persons. Sex ratio for controls is 104 which correlates with the world standards. No sex ratio deviations associated with exposure of the mother or father were established for the Techa cohort members without CRS. A slightly increased number of boys was born in the early years of exposure to fathers with CRS, and, respectively, a slightly larger number of girls was born during the same period to mothers with CRS.

Chapter 11. Mortality Among the Offspring

The analysis of mortality among the offspring of parents with CRS encompasses the period from 1950 through 1989. The information is available on death of 391 persons (16.5%) out of 2,376 children born to parents with CRS. The number of persons who died before 1950 was 216 and in the period 1950-1989 175 persons died. Death certificates are available for 278 deceased persons, the information on the death of 113 was provided by their next-of-kin (by word of moth). Thus, of 1,402 children born after 1949, 175 (12.5%) are deceased.

11.1 Age parameters of mortality

Table 11.1 shows data on the number of death cases among offspring born after 1949 by age at death .

Table 11.1

Number of deceased persons in specific age groups

Age at death	Number of deceased according to relatives (by word of mouth)	Number of deceased confirmed by death certificates	Total number of deceased subjects
0-7 days	0	2	2
8-28 days	0	17	17
28 days -1 year	26	58	84
1 year –2 years	4	9	13
2 years -44 years	22	37	59
All ages	52	123	175

Of 175 deceased persons who died at different ages there were 103 (59%) children who died at the age under 1 year. Death certificates are available for 123 (70.3%) death cases. Seventy-seven (74.8%) death cases among children aged under 1 year were confirmed by death certificates.

11.2 Dynamics of infant mortality

Dynamics of infant mortality (mortality among children under 1 year) is shown in Table 11.2.

Table 11.2

Dynamics of death rates for infants

Periods of	Number of	Number of children	Rate of infant

follow-up	children born	aged under 1 year at death	mortality per 1,000 children born
1950-1954	377	45	119.4
1955-1959	346	31	89.6
1960-1969	466	23	49.4
1970-1979	188	4	21.3
1980-1989	25	0	
1950-1989	1,402	103	73.5

The most clear-cut distinct obvious dependence was a decrease in infant death rates observed from 1950 through the end of the follow-up. During the first decade after the onset of exposure one out of ten children died under the age of 1 year. The death rate among infants estimated for the entire period of follow-up on the basis of all sources of information available was 73.6 per 1,000 children born after the radiation exposure started.

Infant mortality coefficients calculated per 1,000 livebirths for the offspring of patients with CRS were compared with those for exposed parents without CRS, and unexposed persons by time periods (Table 11.3).

It can be seen that a negative temporal trend of infant mortality was determined both for children representing the offspring of CRS patients and offspring of the control population. The estimated coefficients of mortality among children under 1 year and their 95% confidence intervals indicate a slightly higher death rate among offspring of patients with CRS.

Table 11.3

Infant mortality rates estimated for children born to patients with CRS, exposed members of the Techa cohort, and controls

Follow-up periods	Mortality among children of parents	Mortality among children of Techa	Mortality among children of

	with CRS	cohort members	unexposed parents (control)
1950-1954	119.4 (87.0-159.7)	105.5 (96.4-115.1)	91.9
1955-1959	89.6 (60.9-127.1)	62.9 (55.6-70.8)	69.2
1960-1969	49.4 (31.3-74.0)	29.4 (25.3-34.7)	41.3
1970-1979	21.3 (5.8-54.5)		
1980-1989	0		
1950-1989	73.5 (59.9-89.2)		

11.3 Mortality structure

Death causes were analyzed for 123 death cases for which death certificates were available and which occurred among offspring born after the exposure started (Table 11.4).

Death certificates were available for 19 death cases registered among children under 28 days of life (neonatal death), 58 death case among children aged 1 month to 1 year, 9 death cases among children aged 1-2 years, and 37 death cases among children over 2 years (up to 44 years) of age.

In the mortality structure the first place is occupied by diseases of the respiratory organs, the second place by infectious diseases, and traumas rank third among death causes. However, the prevalence of different death causes depends to a large degree on age. Thus, among children who died at the age under 1 year infectious diseases and respiratory disorder account for 50.6% of death causes; congenital anomalies, neonatal diseases and conditions of uncertain etiology account, in total, for 42.8%. Adolescents and young persons most often died from trauma and poisoning, there were 20 death cases (54.0%) from these causes. Infectious diseases (6 cases, 16%) were represented among this age group mostly by different forms of tuberculosis which occurred in the 1950s-1960s.

Table 11.4

Mortality structure for offspring

Death cause, Disease classes	Number of death cases at age under 28	Number of death cases at age from 28	Number of death cases at age	Number of death cases at age

according to ICD-9	days	days to 1 year	1 to 2 years	over 2 years
Infectious diseases		11	5	6
Metabolic disorders		1		
Nervous system disorders		3	1	1
Blood circulation disorders				1
Respiratory disorders	1	27	3	3
Digestive system disorders		1		1
Complications of pregnancy, labor and postpartum period				2
Diseases of osteo-muscular system				1
Congenital developmental defects	1	3		1
Certain conditions originating in the perinatal period	17	4		
Ill-defined conditions		8		1
Injuries and poisoning				20
All causes	19	58	9	37

The infant mortality by most common death causes are shown in Table 11.5. It should be noted that coefficients were estimated only for death cases for which death certificates were available, actual mortality may turn out to be 25% higher.

Table 11.5

Infant mortality for offspring of patients with CRS, exposed persons and controls by most common causes

Death causes , disease classes, according to ICD-9	Offspring of parents with CRS (1,402 persons)	Offspring of the Techa cohort members	Control (23,032 persons)

		(12,206 persons)	
Infectious diseases	7.85 (3.92-14.05)	11.80 (9.94-13.90)	13.33 (11.88-14.90)
Respiratory disorders	20.0 (13.3-29.0)	17.53 (15.22-20.05)	25.44 (23.48-27.62)
Congenital developmental defects	285 (0.77-7.30)	2.21 (1.46-3.23)	1.13 (0.74-1.66)
Certain conditions originating in the perinatal period	14.98* (9.27-22.92)	5.16 (3.96-6.60)	4.17 (3.38-5.09)
Ill-defined conditions	5.71 (2.46-11.24)	4.42 (3.32-5.82)	2.99 (2.33-3.78)
All causes listed above	51.4 (40.16-64.60)	41.12 (37.59-44.87)	47.12 (44.25-50.14)

Note: * indicates statistically significant differences ($p<0.05$).

The analysis focused on infant death from most commonly occurring diseases including the group of exogenous diseases (infectious diseases and respiratory disorders), endogenous death causes (congenital anomalies and certain conditions observed in the perinatal period), as well as ill-defined conditions. The above-indicated pathological conditions account for 93.5% of all causes of infant mortality among offspring of patients with CRS. No significant differences in mortality from causes listed above were found between the three groups compared (offspring of patients with CRS, exposed parents without CRS, and unexposed parents). However, a re-distribution of death causes can be observed towards an increase in the death rates from endogenous causes among the offspring of exposed parents. It is recommended to estimate the total infant mortality rates from endogenous causes since they can serve as the basis for assessment of the impacts of unfavorable environmental factors. The estimated coefficients of mortality from endogenous causes were as follows: 17.83 (95% CI: 11.54; 26.39) for offspring of patients with CRS; 7.37 (95% CI: 5.85; 9.00) for offspring of exposed persons without CRS; 5.30 (95% CI: 4.40; 6.33) for children born to unexposed controls. Thus, cases of death from endogenous causes were registered with significantly higher frequency among offspring of parents with CRS than among offspring of exposed persons and controls. The mortality from congenital developmental defects was estimated to be twice as high and that from certain perinatal conditions and three times as high among children of patients with CRS, compared to controls. The most frequently occurring perinatal conditions included respiratory insufficiency (asphyxia) and convulsive syndrome. Congenital anomalies were represented by chromosome diseases (Down's syndrome) - 1 case, congenital heart defect - 3 cases, multiple developmental defects - 1 case.

11.4 Infant mortality vs intrauterine exposure dose

Pathological conditions observed among offspring of CRS patients exposed on the Techa can be attributed not only to exposure of parental gonads but to intrauterine exposure of the fetus as well. The antenatally exposed group comprised children born to exposed mothers in 1950-1952, a period characterized by the highest annual dose rates. During that period 145 children were born to women diagnosed with CRS. The doses of intrauterine exposure were distributed as follows: doses below 30 mSv were received by 97 children; doses of 30-49 mSv were received by 21 child; doses of 50-99 mSv were received by 9 children; and doses over 100 mSv were received by 18 children. Twenty children died at the age under 1 year. It was possible to estimate infant mortality only for 2 groups with different values of intrauterine doses: below 30 mSv and over 30 mSv (Table 11.6).

Table 11.6

Infant mortality for 1950-1952 by dose of intrauterine exposure

Parameters	Dose of intrauterine exposure < 30 mSv	Dose of intrauterine exposure > 30 mSv
Children born	97	48
Children died at age under 1 year	8	12
Infant mortality rate calculated per 1,000	82.5 (35.5-162.5)	250.0 (129.2-437.5)

The most frequent causes of death in childhood were infectious diseases of the respiratory organs. The excess death cases among children exposed antenatally can be attributed to a deficient anti-infectious immunity [45, 46]. The infant death rate turned out to be higher at higher doses of intrauterine exposure, however, the differences in the parameter under study were statistically insignificant in the dose compared groups, obviously, because of a small size of the sample.

Conclusion

The purpose of the present study was to analyze the reproductive function for individuals exposed in the Techa riverside villages and diagnosed with chronic radiation sickness. The study of the reproductive function was based on a higher sensitivity of the generative cells to radiation exposure and the established fact of the development of temporary or permanent sterility as a result of acute exposure at doses in excess of 0.15 Gy [1].

The population of the riverside villages was exposed to chronic radiation, both external and internal, due to discharges of radioactive waste into the river Techa in 1950-1956. For some residents of the upper Techa annual doses and/or those accumulated during the first decade after the onset of exposure exceeded 1 Gy to red bone marrow. Such doses could cause manifestations of stochastic radiation effects. Among 26 thousand persons exposed in the riverside villages on the Techa there were 940 who were diagnosed with chronic radiation sickness. The studies completed in earlier years [29, 30] focused on analysis of clinical symptoms, course and outcomes of the disease. The present report discusses the reproductive function.

The reproductive function is a system with multiple-level functions, including the function of endocrine glands, maturation of sex cells, fertilization, gestation, birth and development of offspring. In order to correctly evaluate the reproductive function it was necessary to assess the rates of fertility, fetus loss (unfavorable outcomes of pregnancy), health status for newborns. We met with considerable difficulties in organizing the studies and clarifying the question of whether or not the chronic radiation exposure on the Techa had an effect on the reproductive function of patients with chronic radiation sickness. First and foremost, the application of family planning practice made it difficult to answer the question of whether or not radiation exposure had resulted in decreased birth rates. A great influence was exerted on birth rates by social and domestic conditions too.

The group which was used to study the reproductive function was not large, it comprised 940 individuals. The group included 156 persons who were over 50 years at the time the diagnoses of CRS were established, i.e., they attained the age at which the reproductive function is on the decline. The range of doses to gonads was sufficiently wide: from 1,270 mGy to 20 mGy, however, the distribution of doses in the group was ununiform, and the fraction of individuals with doses below 150 mGy accounted for 60%.

It could hardly be expected to find in a small group of exposed individuals a significant increase in genetic disorders, such as autosomal-dominant and X-chromosome linked diseases the rate of which normally does not exceed 1%.

Therefore, in our studies addressing the reproductive function we were guided by the following two principles:

1/ the group of patients with CRS was regarded as a proportion of population exposed on the Techa, and radiation effects were studied both for patients with CRS and for total Techa cohort;

2/ the rate of multifactor pathology, such as spontaneous abortions, stillbirths, early neonatal death, birth of children with developmental defects, were analyzed for exposed residents and their offspring.

It was observed on the basis of studies conducted to assess the prevalence of sex organ diseases involved in the causation of reproductive function disorders that the rate of inflammatory affections among women diagnosed with chronic radiation sickness was rather high, 566 cases per 1,000. There is no grounds to associate this fact with radiation exposure: no dose-effect dependence has been established. Inadequate living conditions, use of outside toilets, numerous abortions were the principal causes which led to a high prevalence of inflammatory processes in female sex organs. In all likelihood, it is to these disorders that the high percentage of infertility, mostly secondary infertility, can be attributed.

Analysis of the menstrual function for those women with CRS who were exposed in childhood showed that cases of delayed menarche occurred among them more frequently than among controls. However, it should be noted that radiation exposure may be regarded only as one of the risk factors accounting for this pathology. Other risk factors which affected the health status of followed-up women included poor social conditions, undernurishment during the first post-war years, i.e., at the time of physical development and sexual maturation. There were no differences in menopausal age for women with CRS compared to controls of matching ages; no dependence of menopausal age on dose to gonads was established. It is in this respect that the data on women exposed on the Techa differ from those on A-bomb survivors.

Most exposed persons with CRS got married. The marriage coefficient accounted for 98.7%, which was even higher than the USSR’s rate according to official statistical data published in 1987. This higher rate may be due to the fact that we based our study not on officially registered marriages but on factual marriages reported by the interviewed people themselves.

The proportion of childless marriages among persons with CRS accounted for a low percentage - 3.64%. The study of past histories of women whose marriages turned out to be childless allowed to assume that infertility may have been caused by extragenital processes in 11% of cases, inflammatory processes in genital organs in 28%, and possible hormonal disorders in 28% of cases. It was impossible to identify even a conjectural cause of infertility for 6 marriages (33%). Linear approximation to relationship between infertile marriages and dose accumulated in the gonads yielded a positive dependence accounted for 2.3% per 1 Sv.

The status of the reproductive function for patients with CRS was also evaluated on the basis of the number of children born. After the onset of exposure 1,402 children were born. It was impossible to calculate the birth coefficient because of the deranged, as compared to a normal population, age structure of the CRS cohort. It was, however, possible to estimate the rate of fertility for women of reproductive age (13-49) diagnosed with CRS. Women with CRS exposed in Chelyabinsk Region gave birth to 699 children in the period from 1950 through 1989. The average fertility rate for this period was estimated as 66.4 per 1,000 women, which was not lower than the respective national value. It can be concluded on the basis of the foregoing that the childbearing function was not affected in women with CRS.

As to potential genetic and teratogenic effects that can be associated with chronic exposure to radiation, it was deemed important to study the health status of the offspring and the rate of loss of offspring for exposed persons with CRS. Teratogenic effects could be manifested only during the period of maximum rates of external doses, i.e., in case pregnancy occurred in 1950-1952, and the fetus was exposed during the entire gestation period. Genetic effects associated with exposure of genital cells were likely to develop as early as the first year of exposure.

The analysis encompassed primarily the incidence of unfavorable outcomes of pregnancy which included cases of spontaneous abortions, stillbirths, death of newborn children within 7 days of delivery and congenital developmental defects diagnosed at maternity homes. This incidence estimated on the basis of the study of labor histories and newborns' development histories accounted for 11.6% (95% CI; 6.79; 18.58) for parents with CRS, and 4.31% (95% CI; 3.02; 5.96) for unexposed parents. However, it should be pointed out that the conclusion about the statistically more frequent unfavorable outcomes of pregnancies among women with CRS is based on the study of only 284 pregnancies for which records were available. The attempt to approximate the dose dependency of unfavorable outcomes of pregnancies among all exposed subjects included in the study resulted in the estimation of the spontaneous rate of pathologic conditions (at 0 dose) as equal to 4.58%. The use of the above-indicated method allowed to identify 3% of additional cases of unfavorable outcomes of pregnancies at exposure dose to gonads equal to 1 Sv. Therefore, the doubling dose can be estimated as 1.53 Sv. It is a rather preliminary and approximate estimation because the dose-effect dependence lacks statistical significance. Our earlier estimates of the doubling dose based on data on unfavorable outcomes of pregnancies in cases of one- or both-parent exposure yielded a wide range of doses (from 0.2 to 4.3 Sv) and pointed to a significant uncertainty of estimates [23].

As to the sex ratio for children born to patients with CRS it can be noted that during the first decade after the onset of exposure the majority of children born to mothers diagnosed with CRS were girls (sex ratio = 92.8), whereas a large number of children born to fathers with CRS were boys (sex ratio = 136.4). This can be regarded, with an essential degree of certainty, as a manifestation of exposure effect, since it is this specific manifestation of deranged sex ratio that was predicted on theoretical basis [12], and was actually observed among the offspring of A-bomb survivors [7].

Physical characteristics of most children born to members of the study cohort were found to be normal. Mean values for body weight, body length and head circumference in children born to patients with CRS did not differ from those registered among children born to control parents. However, in spite of comparable mean body weights children born to CRS patients manifest a wider scatter of values, i.e., the fraction of both children with large body weight and those with small body weight is increased which may be regarded as an evidence of an increased proportion among the offspring of individuals demonstrating inadequate adaptability to environmental hazards [11].

Death rates for children born to patients with CRS were estimated. Infant mortality (mortality among children under 1 year of life) made up 73.5, and it was particularly high in the period 1950-1954: 120 cases per 1,000 neonates. Equally high death coefficients were estimated for the same period for children born to unexposed parents. These processes were a reflection of the impacts of unfavorable living conditions and inadequate standards of medical assistance in the post-war period, particularly in rural localities. No statistically significant differences in death rate were found between children born to patients with CRS and those born to exposed parents without CRS. Among children who were born to parents with CRS and died before they attained the age of 1 year the incidence of infectious diseases and respiratory disorders accounted for 50.6%; congenital anomalies, neonatal disorders and ill-defined conditions constituted in total 42. 8%. A certain re-distribution of death causes can be evidenced with a bias towards increased rate of death from endogenous causes. Compared to controls congenital developmental defects were observed twice as frequently, and fatal outcomes due to specific perinatal conditions occurred 3 times as frequently among children born to parents diagnosed with CRS.

Thus, no disturbances of the reproductive function were detected among exposed individuals with CRS. The cohort of children born to patients with CRS was noted to have a number of specific features which can be interpreted as effects of exposure to ionizing radiation:

- a shift in the sex ratio;
- a large variability of anthropometric characteristics in neonates;
- an increased death rate from specific conditions occurring during the perinatal period.

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